United
for global health

2017-2018 Report

international network
Institut Pasteur

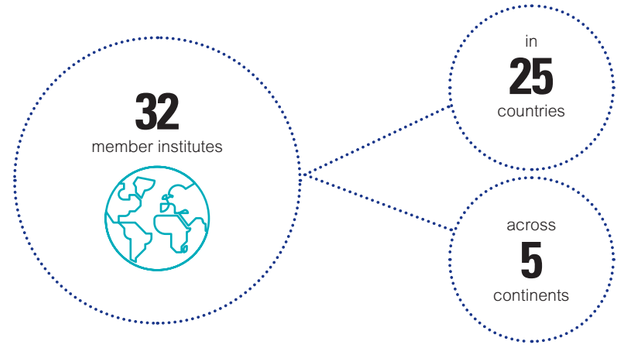
Table of contents

THANKS

We would like to thank all the employees working in the Institut Pasteur International Network, particularly those who accepted to appear in and/or contribute to this report.
We also thank the members of the Institut Pasteur Department of International Affairs for their daily commitment, as well as Marc Jouan, International Vice-President from 2014 to 2018, who joined the Institut Pasteur de Nouvelle-Calédonie in January 2019.
Particular thanks go to Évelyne Malanchère for her commitment, throughout her career, to welcoming foreign delegations, and Olivier Rescanière, International Communications Manager until 2018.
We express our sincere gratitude to all the Institut Pasteur teams in Paris for their assistance and cooperation, and all the partners and institutions whose constant support contributes to the development of cooperation programs within the Network to provide valuable benefits for public health.

The Institut Pasteur International Network

KEY FIGURES



116
scientists and students benefiting from funding of international grants[1]
(see pages 52-53)

25
international courses organized[1]
(see pages 52-53)

5
4-year research groups currently running[1]
(see pages 54-55)

2
International Joint Research Units created[1]
(see page 56)

A SCIENTIFIC NETWORK

4,580
The average number of Web of Science articles published by Network members each year, either individually or in collaboration[1].

1,200
The number of articles uploaded to HAL-RIIP[2], an open platform for archiving and accessing scientific publications[1].

1 Data for 2017-2018.
2 Hyper articles online (HAL).

The Institut Pasteur
International Network

Comprising 32 members, the Institut Pasteur International Network is active on five continents. Leveraging its vast scientific and human community, the Institut Pasteur International Network takes part in national and international research, public health and education programs.

AMERICAS

Brazil
Fiocruz
https://portal.fiocruz.br

Canada
Armand-Frappier Santé Biotechnologie Research center
www.iaf.inrs.ca

France
Institut Pasteur de la Guadeloupe
http://web.pasteur-guadeloupe.fr
Institut Pasteur de la Guyane
www.pasteur-cayenne.fr

Uruguay
Institut Pasteur de Montevideo
www.pasteur.edu.uy/en/home

AFRICA

Cameroon
Pasteur Center in Cameroon
www.pasteur-yaounde.org

Ivory Coast
Institut Pasteur de Côte d'Ivoire
www.pasteur.ci

Guinea
Institut Pasteur de Guinée
www.pasteur-guinee.org

Madagascar
Institut Pasteur de Madagascar
www.pasteur.mg

Niger
CERMES
www.cermes.net

Central African Republic
Institut Pasteur de Bangui
www.pasteur-bangui.org

Senegal
Institut Pasteur de Dakar
www.pasteur.sn

EUROPE

Belgium
Sciensano
www.sciensano.be

Bulgaria
Stephan Angeloff Institute of Microbiology
www.microbio.bas.bg

France
Institut Pasteur (Paris)
www.pasteur.fr
Institut Pasteur de Lille
www.pasteur-lille.fr

Greece
Hellenic Pasteur Institute
www.pasteur.gr

Italy
Institut Pasteur in Italy – Cenci Bolognetti Foundation
www.istitutopasteur.it

Russia
Institut Pasteur in Saint-Petersburg
www.pasteurorg.ru

NORTH AFRICA-IRAN

Algeria
Institut Pasteur d'Algérie
www.pasteur.dz

Iran
Institut Pasteur in Iran
http://en.pasteur.ac.ir/

Morocco
Institut Pasteur du Maroc
www.pasteur.ma

Tunisia
Institut Pasteur de Tunis
www.pasteur.tn

ASIA-PACIFIC

Cambodia
Institut Pasteur du Cambodge
www.pasteur-kh.org

China
Honk Kong University-Pasteur Research Pole
www.hkupasteur.hku.hk
Institut Pasteur of Shanghai – Chinese Academy of Sciences
www.shanghaipasteur.cas.cn

Korea
Institut Pasteur Korea
www.ip-korea.org

France
Institut Pasteur de Nouvelle-Calédonie
www.institutpasteur.nc

Laos
Institut Pasteur du Laos
www.pasteur.la

Vietnam
National Institute of Hygiene Epidemiology (Hanoi)
https://nihe.org.vn
Institut Pasteur in Ho Chi Minh City
www.pasteurhcm.gov.vn
Institut Pasteur in Nha Trang
http://pasteur-nhatrang.org.vn/

Stewart Cole

President of the Institut Pasteur

> The development of the Institut Pasteur International Network is one of my priorities.

The 2019-2023 Strategic Plan is a clear reflection of this. The scientific collaborations the Institut Pasteur conducts with its 32 International Network partners provide a concrete response to global health challenges. Together, they have been able to develop the scientific synergies that are key to leveraging advances made in fundamental research for the good of public health.
With the support of the Institut Pasteur, the Network has been able to take action against the recent health crises (Ebola, Zika) that have seriously affected different continents.
I also wish to strengthen the attractiveness of the Network by supporting the participation of its researchers in major international projects, encouraging openness across its institutes to pool resources (bioinformatics, biobanks, vectopole, imaging) and emphasizing their attractiveness to international researchers. I am confident in the Institut Pasteur International Network's capabilities to draw inspiration from shared scientific ambitions, taking into account the diversity of scientific and political environments, to increase the visibility and impact of its research in global health.

The Institut Pasteur Department of International Affairs will continue its efforts to strengthen the competitiveness and visibility of the Institut Pasteur International Network. The history that Pasteur institutes share commits us to advancing further, building on high-quality research, training opportunities and the provision of public health, particularly to vulnerable populations. Through a collaborative approach in line with the Network's scientific strategy, approved by the Council of Directors in September 2017, the Network will develop major international initiatives to position itself as a leading global player as regards global public health challenges. These programs will leverage knowledge and scientific expertise in the fields of prevention and treatment for the benefit of local populations. The Department of International Affairs will also continue its active policy of creating 4-year research groups (G4) to encourage talented young scientists to return to the countries in which the institutes are located. Active in 25 countries across 5 continents, the Network acts to combat emerging diseases. This represents an outstanding base from which to develop international scientific cooperation.

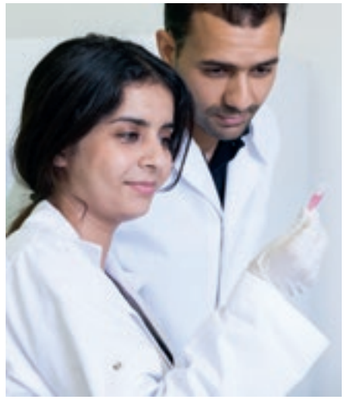
> The Network will develop large-scale initiatives worldwide to position itself among international players.

Pierre-Marie Girard

International Vice-President, Institut Pasteur

Missions and organization

OF THE INSTITUT PASTEUR INTERNATIONAL NETWORK



Active in 25 countries across 5 continents, the Institut Pasteur International Network ("the Network") brings together 32 institutions united by the Pasteurian values and missions for the benefit of local populations. A unique model of cooperation in the field of health, the Network brings together men and women who contribute on a daily basis to the fight against infectious diseases, through biomedical research, public health activities and training. With a strong foothold at the heart of several areas struck by endemic and epidemic diseases, time and again the Network has demonstrated the key role it plays as a watchdog in the face of infection-related emergencies.

The mission of the Institut Pasteur International Network is to contribute to the improvement of human health, in particular relating to infections, through:

- **biomedical research;**
- **public health activities;**
- **training;**
- **innovation and technology transfer.**

These activities are carried out with a view to promoting sustainable development, based on developing local capabilities with respect for human rights and the environment.

The 32 member institutes of the Institut Pasteur International Network, partners and associates in scientific research, public health services and education alliances, have signed the **Institut Pasteur International Network Cooperation Agreement**, which includes a Charter of Pasteurian Values adopted by all members of the network. These values include humanitarianism, universalism, rigor and dedication, freedom of initiative, the dissemination of knowledge and free access to information. According to the Agreement, the Network is founded on scientific solidarity, meeting national and international needs, contributing to education and involvement in global public health issues.

The **Council of Directors of the International Network** is made up of the directors of each member institute. Chaired by the President of the Institut Pasteur in Paris, the Board meets once or twice a year and elects twelve representatives at the Institut Pasteur's General Meeting. When they meet, the Directors establish and approve the main development priorities for the Network and its procedures.

Since it was founded, the Institut Pasteur has acted on a global scale. The International Vice-President of the Institut Pasteur is tasked with coordinating the Network's joint activities. These activities are implemented by the Department of International Affairs, which oversees major research and public health programs involving the Network, manages funds supporting mobility (Calmette & Yersin program, 4-year research groups) and participates in training programs within the Network. Participation in the board of directors' and scientific council meetings of Network member institutes is conducted in close contact with the Department of International Affairs. This Department also manages funding and the secondment of personnel to certain institutes from the Institut Pasteur in Paris, with the backing of the French Ministry of Foreign Affairs and International Development and the Ministry for Higher Education, Research and Innovation.

Development of the Network:

A CROSS-FUNCTIONAL PRIORITY IN THE NEW INSTITUT PASTEUR STRATEGIC PLAN

The Institut Pasteur is firmly committed to carrying out its work to improve human health worldwide as part of an ambitious international strategy centered on the Institut Pasteur International Network.

After taking office as President of the Institut Pasteur in January 2018, Professor Stewart Cole devised a new Strategic Plan 2019-2023 for the Institut. On December 21, 2018, the Board of Directors unanimously adopted this ambitious yet realistic action plan for the next five years.

As part of this plan, one of the cross-functional priorities of the Institut Pasteur's strategy will be to strengthen the Institut Pasteur International Network and develop partnerships with key institutions outside the network.

To support this ambition and unite scientific teams, several objectives are directly associated with this cross-functional priority:

- **Structure and strengthen relationships with the International Network based on shared scientific ambitions *(see pages 8-9).***
- **Build the Network's influence by working towards a more structured governance framework and business model.**
- **Increase the Institut Pasteur's attractiveness internationally.**

The Institut Pasteur International Network constitutes a major asset for responding to the major issues involved in health research.
This Network, composed of 32 partner institutes spread across five continents, is unique and represents an outstanding base from which to develop international scientific cooperation.

Collaborative research is a means of guaranteeing scientific excellence by comparing and exchanging ideas.

Biomedical research is facing major challenges in the 21st century, including the emergence of new epidemics, the development of resistance to anti-infective agents, health conditions associated with increased life expectancy, the constant rise in cancer incidence, global warming, and globalization with all its implications. Against this backdrop, the Network, which is active in 25 countries, encourages the mobilization of its institutes to deal with health challenges and emerging infections.

The Institut Pasteur will endeavor to consolidate its Network into a more coherent entity, represented by the Pasteur International Network association, to ensure that its action reflects a culture of international solidarity. It will work to promote scientific leadership in the Network to tackle various specific global health challenges.

Extracts from the Institut Pasteur Strategic Plan 2019-2023:
https://www.pasteur.fr/fr/espace-presse/documents-presse/nouveau-plan-strategique-2019-2023-institut-pasteur

THE PASTEUR INTERNATIONAL NETWORK association

The Pasteur International Network Association, founded in 2011 under the 1901 French law, is the legal entity of the Institut Pasteur International Network. Its membership is made up of the Network institutes located around the world. It shares the Network's missions *(see page 5)* in fighting infectious diseases.

Enshrined within the Institut Pasteur International Network collaboration agreement, its mission is to *"facilitate the development and implementation of large-scale scientific training projects and actions, generally with the participation of several members of the Network"*.

From its annual budget, funded by the contributions of its members, it finances international courses and the organization of regional meetings on the five continents. The association is an operational platform able to participate in the implementation of cross-functional scientific activities, assistance with governance and the application of research for the communities concerned, regional decision-makers and the general public.

The regions are defined in connection with the geographical distribution of the Network's institutes: Africa-Indian Ocean, the Americas, Asia-Pacific, Europe, North Africa-Iran.
The association, chaired by the President of the Institut Pasteur, has two governing bodies:

- **a General Meeting, bringing together all the directors of the member institutes, which meets every year.**
- **a Board of Directors, comprising representatives of member institutes, elected by region, and representatives of the Institut Pasteur and co-opted external members. The Board of Directors meets twice a year.**

A NON-STATE ACTOR IN OFFICIAL RELATIONS WITH THE WORLD HEALTH ORGANIZATION (WHO)

Pasteur International Network association was recognized as a "non-State actor in Official Relations" with the WHO in 2016.
In 2018, the association supported three statements at the 71st World Health Assembly, which took place in Geneva from May 21 to 26, 2018. The first statement supported the program to combat the global shortage of effective and affordable quality medicines and vaccines and to promote access to them. In the second statement, it expressed its concerns about the achievement of the objectives to stop TB.
Finally, the last statement supported the vision and objectives set out in WHO's new General Program of Work 2019-2023.
Of particular note, the fight against emerging epidemics and antimicrobial resistance, and promoting better support for research and development, as well as better access to medicines, vaccines and diagnostics.

A shared scientific strategy

TO DRIVE HOME THE NETWORK'S GLOBAL HEALTH AMBITIONS

In 2017, the Institut Pasteur International Network adopted an ambitious scientific strategy in order to strengthen its position and promote its role as a global actor in public health. Four key scientific priorities have been identified, stemming from an in-depth analysis of the specificities and assets of this unique, constantly evolving Network. This strategy will evolve to adapt to new challenges on the global level.

A COLLECTIVE STRATEGIC THOUGHT PROCESS

During the 48th Directors' Council at the Château des Ravatys (France) in May 2016, a willingness was expressed for the Network's actions to better reflect the global dimension it has taken on, through setting objectives with global meaning, driven by ambitious collaborative programs with a strong impact on the health of local populations. A collective effort, coordinated by the Department of International Affairs, was carried out by the Network's Scientific Committee for Strategy and enhanced through an online consultation involving the Network's scientists. The 49th Directors' Council, which took place in Abidjan in September 2017, endorsed the vision of the Network's scientific strategy and the objectives set for the years to come.

THE NETWORK: A GLOBAL ACTOR

Over more than 130 years, the Network has grown, diversified and spread to 25 countries across 5 continents. It aims to work towards a more structured model and consolidate its position as a major player in research and public health worldwide. To do so, it must spearhead a number of major cross-functional programs, taking advantage of the scientific, technological and operational expertise of the Network's institutes. To develop a "problem-solving" approach, it will draw on a proactive analysis of the target health challenge and its diversity of expression depending on the area. It will identify persistent information gaps to be filled and the obstacles perpetuating health problems that must be overcome.

A SCIENTIFIC STRATEGY LEVERAGING THE ASSETS OF THE NETWORK

The global distribution of the Network gives its teams access to an immense range of geoclimates, ecosystems, socioeconomic situations, cultures and biologies (human and animal), which impact the diversity of infections and/or pathogens, their transmission and their conditions of emergence or endemic continuation. The long tradition of exchange and collaboration between members of the Network facilitates the establishment of multi-site programs and coordinated comparative studies to explore these levels of diversity. The wide range of scientific and technological expertise available within the Network makes it possible to utilize cutting-edge techniques. It facilitates the design and development of diagnostic tools and adapted preventive and curative solutions, and their on the ground implementation.

BASED ON THESE OBSERVATIONS, FOUR KEY SCIENTIFIC PRIORITIES HAVE BEEN IDENTIFIED:

- **1. Exploring the principal endemic and emergent zoonoses according to a *one health* approach.**
  Studies will target the pathogen, any vectors it may have, humans and domestic and wild reservoir animals, as they evolve in their various ecosystems, either natural or transformed by humans. Particular interest will be paid to neglected tropical infectious diseases (rabies, leptospirosis, etc.), the study of antimicrobial resistance, and emerging/related infections to map their distribution across different ecosystems.

- **2. Studying vector-borne infectious disease,**
  with a focus on the biology of vector insects, their genetic diversity, pathogen-vector interactions, the natural history of infection in humans and animals based on individual factors, the dynamics of installation in newly invaded territories and determining factors.
  The increasingly limited context of the anti-vector fight justifies the study of innovative vector control strategies.

- **3. Exploring the risk of infection in the first years of life, particularly in marginalized and migrant populations.**
  During the pre- and peri-natal periods: studying the maternofetal transmission of infection. During childhood: studying the impact of malnutrition, respiratory infections, diarrhea and encephalitis on neurological and cognitive development and growth. During adolescence: studying the health risks specific to this period of transition.

- **4. Studying the impact of aging/longevity on health.**
  Chronic diseases such as metabolic syndromes, cancer, genetic diseases, neurodegenerative conditions, inflammatory diseases.

SUPPORT ACTIVITIES TO STRUCTURE THE NETWORK

The success of the scientific strategy depends on the pooling of resources and data, and the sharing of technological platforms *(see pages 57 to 59)*. The establishment of a network of biobanks for the conservation of samples for analysis (PIBnet project) contributes to this pooling of resources.
A certified multi-format life sciences training program specifically focuses on bioinformatics, biostatistics, epidemiology, conducting clinical trials and preparing for emerging epidemics. This will be supported by the strengthening of cross-functional programs, the mobility of researchers across institutes and the establishment of 4-year research groups. The Institut Pasteur International Network Scientific Steering Committee has been created to monitor the implementation of this strategy.

"The consolidation of the shared scientific life of the Network is in the interest of each institute, above and beyond the national missions it takes on. It gives the observations made in the highly diverse context of the Network the sufficient level of objectivity, which makes them even more significant and notably showcases local and regional specificities.

Koussay Dellagi, Scientific Strategy Coordinator for the Network

Highlights 2017

JANUARY

A mobile insectarium to combat malaria

In Cambodia, the parasites the most resistant to the new generation of antimalarials are widespread. Thanks to the support of the Rotary Club of Versailles and the Rotary Club of Phnom Penh, the Institut Pasteur du Cambodge now has a mobile insectarium to enable them to conduct research activities and entomology training with the most affected populations in rural areas.

MARCH

UNIVERSITY OF HONG KONG – PASTEUR RESEARCH POLE RENEWED FOR 10 YEARS

Founded in 1999, this research and training center within the Public Health School at the University of Hong Kong Li Ka Shing Medical Faculty, focuses on host-pathogen interactions, particularly with regard to respiratory viruses.

HEALTH AND ENVIRONMENT LAUNCH OF THE ECOMORE 2 PROJECT

Financed by the French Development Agency (AFD) for up to 4 million euros for 3 years, this project will study the impact of ecosystem changes on population health due to human activities and climate change in five south-east Asian countries (Cambodia, Laos, Vietnam, Myanmar, Philippines).

MAY

Insecticide resistance detected in malaria-bearing mosquitoes in Bangui

Work carried out in the Central African Republic by researchers from the University of Denver in the USA, Abomey-Calavi in Benin and the Institut Pasteur de Bangui 4-year research group shows that malaria-bearing *Anopheles gambiae* are resistant to DDT and pyrethroids. This resistance is a threat to the antivector fight. Results published in *Parasites and Vectors*.

JUNE

MosKeyTool: a free interactive tool for mosquito identification

The identification of mosquitoes is a key step for the surveillance and control of the diseases for which they are vectors. As part of the Medilabsecure project, free software has been developed to identify the 128 species of mosquitoes recorded in Europe and the Mediterranean Basin. Funded by the European Commission, MediLabSecure aims to build capacity within a network of laboratories working on emerging viruses in 22 countries of the Mediterranean and the Black Sea region *(see pages 22-23)*.

AUGUST

Dengue – Understanding the mechanisms that prevent the development of symptoms following infection

Scientists from the Institut Pasteur in Paris and the Institut Pasteur du Cambodge, in collaboration with teams from the CNRS and Inria, have demonstrated that asymptomatic dengue infection in children is associated with activation of the immune system via control mechanisms, resulting in the elimination of viral infection without excessive immune activation. This paper, published in the scientific journal *Science Translational Medicine*, is an important step in improving understanding of the role played by immunity in dengue viral infection and developing new vaccine strategies.

FIGHTING PLAGUE IN MADAGASCAR

A particularly severe plague outbreak hit the island from August to late November, killing over 200 people. Working alongside health authorities and the World Health Organization, the Institut Pasteur de Madagascar, supported by the Institut Pasteur (in particular the Emergency Biological Intervention Unit, the Yersinia unit and the Center for Global Health) was at the forefront of the response *(see pages 28-29)*.

Persistence of Zika virus in semen

In a paper published in the *The New England Journal of Medicine*, teams from the Institut Pasteur de la Guyane show that the Zika virus is present in semen for a duration of up to 30 to 45 days maximum following the onset of symptoms in 58% of patients infected, and up to 188 days in one individual. In parallel, in a paper published in *The Lancet Infectious Diseases*, teams from the Institut Pasteur in Guadeloupe demonstrated the presence of the virus for a short time in the serum and urine of volunteers and confirm a persistence in semen for up to 120 days in some patients.

Highlights 2017

Institut Pasteur International Network agrees on a scientific strategy

This collaborative strategy aims to promote the international visibility of the Network through unifying cross-functional programs for research into global health challenges. It comprises four major priorities: the implementation of a *one health* approach for exploring the principal endemic and emergent zoonoses, the investigation of vector-borne infectious diseases, the study of mother-child health and other health challenges in children, and the impact of aging/longevity on health including chronic diseases *(see pages 8-9)*.

SEPTEMBER

PASTEUR *INTERNATIONAL TALENT* AWARDS

Dr. Anubis Vega Rua (entomology) from the Institut Pasteur de la Guadeloupe and Dr. Felipe Trajtenberg (molecular and structural microbiology) from the Institut Pasteur de Montevideo are the first laureates of this award, which aims to recognize and support the career development of researchers with high potential within the Institut Pasteur International Network.

49th INSTITUT PASTEUR INTERNATIONAL NETWORK DIRECTORS' COUNCIL IN ABIDJAN

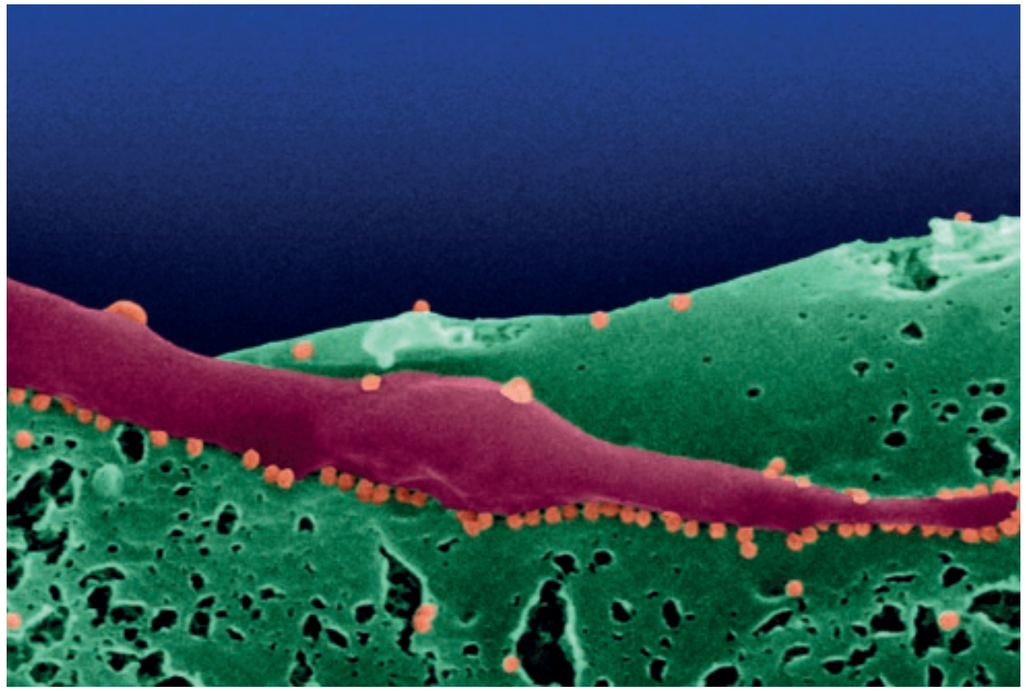
The annual Institut Pasteur International Network Directors' Council took place from September 20 to 22, 2017, in Abidjan. Over three days, representatives of the 32 members institutes were able to take stock of the main development priority areas of the Network. The importance of managing and monitoring the careers of researchers in the network was underlined, as was the need to strengthen collaborations between institutes. During the Council, the Dedonder-Clayton Prize was awarded to Dr. Richard Njouom, head of the virology department at the Pasteur Center in Cameroon, in recognition of his work on viral hepatitis.

OCTOBER

THREE PROJECTS SELECTED FOR FUNDING BY AESA'S GRAND CHALLENGE AFRICA

Two teams from the Institut Pasteur de Dakar and one from the Institut Pasteur in Madagascar are among the eight innovative projects selected by the African Academy of Sciences and the Alliance for Accelerating Excellence in Science in Africa (AESA). The objective is to improve maternal, neonatal and child health in Africa.

OCTOBER



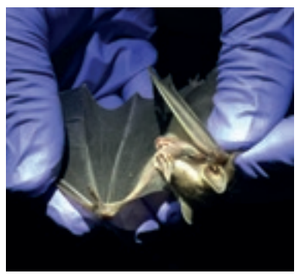
A Pasteur International Joint Unit to understand virus evolution

Co-directed by Prof. Marco Vignuzzi, Head of the Viral Populations and Pathogenesis Unit at the Institut Pasteur and Prof. Ben tenOever, director of the Virus Engineering Center for Therapeutics and Research at the Icahn School of Medicine at Mount Sinai (New York), this Pasteur International Joint Unit will develop a program combining the study of the natural evolution of viruses with synthetic biology to better combat emerging infectious diseases.

THE INSTITUT PASTEUR INTERNATIONAL NETWORK ENTERS THE GLOPID-R ALLIANCE

The Institut Pasteur International Network has officially become a member of the *Global Research collaboration for infectious diseases preparedness research alliance* (GloPID-R). GloPID-R is a network comprising 27 research and research funding organizations globally as well as WHO. The goal of this alliance is to ensure that research capabilities are in place to support the rapid initiation of scientific research in case of an infectious disease outbreak.

NOVEMBER



Viral diversity in two species of bat

Researchers from the Institut Pasteur de la Guyane, in collaboration with the Institut Pasteur and the INRA (French National Institute for Agricultural Research), have shown a significant viral presence in two species of bat in contact with humans in French Guiana. These data are essential as bats are reservoirs for numerous viruses. specifically those responsible for severe diseases (rabies, SARS, Ebola, etc.).

Highlights 2018

JANUARY

TWELVE NEW SPECIES OF *LEPTOSPIRA* DISCOVERED IN NEW CALEDONIA

A group of researchers from the Institut Pasteur International Network coordinated by the Institut Pasteur de Nouvelle-Calédonie has described 12 new species of the genus *Leptospira*. Leptospirosis is a re-emerging zoonosis that affects over one million people and is responsible for nearly 60,000 deaths each year worldwide *(see pages 44-45)*.

FIRST INFECTION PLATFORM FOR MALARIA-BEARING ANOPHELES MOSQUITOES IN MADAGASCAR

Located in the northwest of the island, an area with a medium to high prevalence of malaria, the platform works from November to May and is intended to analyze the vector competence of malaria-bearing Anophele populations.

FEBRUARY

First results of BIRDY project on incidence of neonatal infections

In 2012, the Institut Pasteur and the Institut Pasteur de Madagascar launched the BIRDY program aimed at documenting, at a community level, neonatal infections and assessing the state of antibiotic resistance.
The first results, reported in February 2018, show an extremely high incidence of these infections, 40 times higher than that observed in the USA *(see pages 36-37)*.
The Institut Pasteur du Cambodge joined the program in 2014 with Senegal.

MARCH

A GLOBAL MAPPING OF ZIKA-BEARING MOSQUITOES

A group of entomologists from five member institutes of the Institut Pasteur International Network (Institut Pasteur, Institut Pasteur of Cambodia, Institut Pasteur of New Caledonia, Fiocruz, Institut Pasteur of Dakar) have published a review summarizing the literature on the main vectors of Zika virus in urban and jungle environments on all continents in *Microbes and Infections*.

MARCH

Institut Pasteur de Lille researchers explore the origins of BCG

After the discovery of BCG by Albert Calmette and Camille Guérin, researchers at the Institut Pasteur de Lille (Inserm, CNRS, University of Lille) have opened tubes containing the original strains for genome sequencing. This will contribute to advancing knowledge for the development of a new version of the vaccine that will be more effective against tuberculosis.

APRIL

INAUGURATION OF SCIENSANO, A *ONE HEALTH* RESEARCH INSTITUTE IN BELGIUM

Resulting from the merger of the ex-Scientific Institute of Public Health (ISP - member of the Institut Pasteur International Network) and the Veterinary and Agrochemical Research Center (CERVA), Sciensano made its debut in the Belgian health landscape on April 1st , 2018.
Its activities are guided by the intrinsic association of human health, animal health and the environment.

WHO RECOMMENDS THE INSTITUT PASTEUR DU CAMBODGE RABIES VACCINE REGIMEN

Based on immunogenicity data and clinical effectiveness, the post-exposure anti-rabies vaccine regimen developed by the Institut Pasteur du Cambodge, based on three visits comprising two doses of vaccine given intradermally on days 0, 3 and 7, is recommended by WHO. The Institut Pasteur du Cambodge opened its second rabies prevention center in Battambang in collaboration with the Battambang provincial health department in July 2018, with the objective of vaccinating 10,000 people bitten per year *(see pages 42-43)*.

MAY

A PASTEUR-USP SCIENTIFIC PLATFORM IN BRAZIL TO TACKLE NEUROLOGICAL DISORDERS

A group of scientists have set up the first research team in Brazil under the tripartite University of São Paulo/Institut Pasteur/Fiocruz agreement signed in 2015.
This scientific platform will focus on neurological disorders caused by either infectious agents or degenerative/ progressive diseases.

Launch of H2020 LeiSHield-MATI project in Tunis

Financed by the European H2020 program, the project coordinated by the Institut Pasteur in Paris focuses on cutaneous leishmaniasis. Its objective is to gain scientific knowledge on parasite-vector-host interaction to allow future development of new therapeutic and preventive measures. The institutes of the Network in Algeria, Morocco, Tunisia and in Iran are partners in this project *(see pages 46-47)*.

Highlights 2018

AUGUST

CHRONIC MALNUTRITION IN CHILDREN: A NEW MICROBIAL SIGNATURE IN THE GUT

The Afribiota project, led by several Network institutes (Paris, Madagascar, Bangui), was set up to advance our understanding of the underlying mechanisms of chronic malnutrition. In malnourished children, researchers found the existence of a surprising microbial signature in the gut, characterized by the widespread presence of bacteria that are normally found in the nose and mouth *(see pages 48-49)*.

SEPTEMBER

Titan Krios™: inauguration of the most powerful microscope in the world at the Institut Pasteur

The Institut Pasteur inaugurated the installation of a new electronic microscope with extraordinary capacities: the new Titan Krios™. This new equipment was inaugurated by Frédérique Vidal, Minister of Higher Education, Research and Innovation, Christian Vigouroux, Chairman of the Institut Pasteur Board of Directors, and Stewart Cole, President of the Institut Pasteur. This microscope facilitates the very high resolution observation of the most fragile of samples in as close to their natural conditions as possible, particularly owing to the preparation of these samples using cryogenic techniques.

TWELVE YEARS OF COLLABORATION WITH THE AMERICAN DHHS ON EPIDEMIC SURVEILLANCE AND RESPONSE

With the support of the DHHS (US Department of Health and Human Services), through the ASIDE (Alerting and Surveillance for Infections Disease Epidemics) project, the Institut Pasteur and the Network are supporting six countries in Africa and South-East Asia in order to develop and strengthen capacities for preparing for and responding to epidemics of influenza and emerging or re-emerging infectious diseases, in line with International Health Regulations (2005). During a meeting organized in Washington D.C. in September 2018, the parties involved took stock of the 12-year partnership and contemplated the future of this collaboration *(see page 24)*.

Collaboration in Hong Kong for the creation of a biomedical research center

The University of Hong Kong, the Institut Pasteur and Hong Kong Science and Technology Parks Corporation signed a Memorandum of Understanding in Paris to set up a joint biomedical research center, witnessed by a high-level delegation led by The Hon Mrs Carrie Lam, the Chief Executive of the Hong Kong Special Administrative Region, and Mr Nicholas W Yang, the Secretary for Innovation and Technology.

OCTOBER

Institut Pasteur de Guinée inaugurates its first laboratory in Conakry

The first laboratory of the Institut Pasteur de Guinée was officially inaugurated on October 22, 2018 in the presence of four Guinean ministers and the French Ambassador to Sierra Leone and Guinea. Housed free of charge within the Gamal Abdel Nasser University of Conakry, the "Pasteur Laboratory" is dedicated primarily to public health, monitoring and research activities. Thanks to the support of the Ministry of Europe and Foreign Affairs and Expertise France under the LAB-NET program, 230 m^2 have been transformed into a modern training and research platform for the benefit of Guinea. An expert laboratory for molecular diagnosis of emerging pathogens, the Pasteur laboratory will act to support the national network of laboratories *(see page 26)*.

NOVEMBER

COMBATING RESISTANCE: MICROBES AND VECTORS SYMPOSIUM

The 4th edition of the Institut Pasteur International Network Symposium, which took place on November 15 and 16, 2018 at the Institut Pasteur, brought together almost 350 participants from all over the world. The event included various presentations on the topic of microbe and vector resistance by members from across the Network. Prior to this, the annual **Institut Pasteur International Network Directors' Council** took place from November 13 to 14, 2018, in Paris. Over two days, representatives of the 32 members institutes were able to take stock of the main development priority areas of the Network.

DIDIER KOUMAVI EKOUEVI LAUREATE OF THE DEDONDER-CLAYTON PRIZE 2018

During the 41st Institut Pasteur International Network Scientific Symposium, Dr. Didier K. Ekouevi was awarded the Dedonder-Clayton Prize 2018.
Head of the Public Health Department at the University of Lomé, Togo, Dr. Ekouevi was recognized for his work on the epidemiology of the human *papillomavirus* and the sexually transmitted infections associated with this virus, and for his studies of HIV in Africa.

DECEMBER

AIDS: an approach for targeting HIV reservoirs

Current HIV treatments need to be taken for life by those infected as antiretroviral therapy is unable to eliminate viral reservoirs lurking in immune cells. Institut Pasteur researchers have revealed, in the journal *Cell Metabolism,* that they have been able to identify the characteristics of CD4 T lymphocytes that are preferentially infected by the virus – it is their metabolic (or energy-producing) activity1 that enables the virus to multiply. Thanks to metabolic activity inhibitors, the researchers have managed to destroy these infected cells, or "reservoirs", *ex vivo*.

A PARTNERSHIP FOR THE RECONSTRUCTION OF THE NATIONAL HEALTH LABORATORY IN MYANMAR

The French Development Agency (AFD), the Institut Pasteur and the Mérieux Foundation have made a joint commitment to a €27m project to establish a high-security national reference laboratory in Rangoon, Myanmar. This will reinforce diagnostic capacities in order to better protect the population, in particular the most vulnerable populations, from epidemics and emerging diseases. A European Union grant delegation agreement for €5m for the Institut Pasteur was signed by the AFD and the Institut Pasteur on December 21, 2018, in parallel with the signing of an MoU between the Mérieux Foundation and the AFD for the same project.

National and international **technical expertise**

The Network is home to a large number of national, regional and international laboratories for infectious diseases and antimicrobial resistance.

National and regional reference laboratories are recognized by national health authorities for their expertise in the field of diagnostics. National reference centers act as monitoring centers for transmissible diseases in the countries in which they are situated.

WHO collaborating centers are institutions, research institutes, university departments and university institutes that carry out support activities for Organization programs. They work with WHO in a wide range of fields including nursing care, occupational help, transmissible diseases, nutrition, mental health, chronic diseases and health technology[1].

	WHO COLLABORATING CENTERS	REGIONAL REFERENCE LABORATORIES
Pasteur Center in Cameroon		Bacteriology, avian influenza, food-borne infections, poliomyelitis
Institut Pasteur de Bangui		Poliomyelitis
Institut Pasteur de Côte d'Ivoire		Influenza, poliomyelitis, measles, rubella, gonococcus (resistance) Reference laboratory for the West African Health Organization (WAHO)
Institut Pasteur de Dakar	Arboviruses and viral hemorrhagic fevers FAO reference center for antimicrobial resistance	Avian influenza, WHO regional reference laboratory for poliomyelitis
Institut Pasteur de Madagascar	Plague (under renewal June 2019)	
CERMES (Niger)		Meningitis, influenza, cholera, resistance to antimalarials
Institut Pasteur du Cambodge		WHO reference laboratories H5 influenza
NIHE (Vietnam)		
Institut Pasteur de la Guadeloupe		
Institut Pasteur de la Guyane	Drug resistance of malaria[2]	
Hellenic Pasteur Institute		Leishmaniasis, *Neisseria gonorrhoeae*
Institut Pasteur in Saint-Petersburg		Poliomyelitis, yersiniosis, viral hepatitis, measles, rubella, rickettsiae, salmonella, AIDS, typhoid fever surveillance
Sciensano (Belgium)		*Neisseria meningitidis*, botulism, *C. perfringens* and *C. tetani*, food-related microbiology, food-borne diseases, nirovirus, listeriosis, *salmonella*, *shigella*, tuberculosis and mycobacteria, toxoplasmosis, viral hepatitis, human papillomavirus, *Bordetella pertussis*, diphtheria, influenza, measles, rubella, mumps, rabies, *Coxiella burnetii*, *Brucella spp.*, *B. anthracis*, *Burkholderia mallei* and *pseudomallei*, *Francisella tularensis*, *Yersinia pestis*
Institut Pasteur d'Algérie		
Institut Pasteur du Maroc		Tuberculosis (reference for the Casablanca-Settat region)
Institut Pasteur in Iran		
Institut Pasteur de Tunis		Poliovirus, measles, human papillomavirus
Oswaldo Cruz Foundation (Fiocruz)	Global health and South-South cooperation, public and environmental health, leptospirosis, pharmacological policies, training of health technicians	Malaria, dengue, hantaviruses, yellow fever, rotavirus, visceral leishmaniasis, chikungunya, Zika virus

1 https://www.who.int/fr/about/who-we-are/structure/collaborating-centers
2 In the Antilles-Guiana region.
3 WHO-NIC national center.
4 The NRC is part of the Emerging Viral Infections Unit at the International Center for Infectiology Research (Lyon).

NRC AND WHOCC UNDER THE RESPONSIBILITY OF THE INSTITUT PASTEUR (PARIS)

- Anaerobic bacteria and botulism (NRC)
- Whooping cough and other Bordetella (NRC)
- Corynebacterium *diphteriae* (NRC)
- *Escherichia coli*, *Shigella*, *Salmonella* (NRC, WHOCC for *Salmonella)*
- Viral hemorrhagic fevers (NRC, WHOCC)[4]
- *Hantaviruses* (NRC)
- Leptospirosis (NRC)
- *Listeria* (NRC, WHOCC)
- Meningococcal infections and *Haemophilus influenzae* (NRC, WHOCC)
- Invasive mycoses and antifungals (NRC)
- Plague and other yersinia bacteria (NRC)
- Rabies (NRC, WHOCC)
- Vibrio and cholera (NRC)
- Viral respiratory infections, including influenza (NRC)
- Enterovirus and viral vaccines (WHOCC)

NATIONAL REFERENCE LABORATORIES
Influenza[3], yellow fever, measles, monitoring of antibiotic resistance of gonococci
Measles, rubella, arboviruses and hemorrhagic fevers, rabies, influenza[3], mycobacteria, HIV/AIDS
Poliomyelitis, rabies, influenza[3] and respiratory viruses, measles, yellow fever, hemorrhagic fevers, drug resistance of malaria, viral hepatitis, agents of sexually transmitted infections, cholera and shigellosis, bacterial meningitis, salmonella, tuberculosis, Buruli ulcer, diarrhea viruses Ivory Coast Monitoring Center for Resistance to Anti-Infectives (ORMICI) Ivory Coast Network for Investigation and Surveillance of Nosocomial Infections (RIISIN) Evaluation of microbiological diagnostic tests, biological control of antimicrobial vaccines
Influenza[3] and respiratory viruses, measles, rabies, rotavirus and enterobacteria
Vibrio cholerae, salmonella and shigella, mycobacteria, influenza[3], avian influenza, poliomyelitis, measles and rubella, arboviruses and hemorrhagic fevers, rabies Antibiotic resistance monitoring Food and water quality control laboratory
Meningitis, influenza, cholera, resistance to antimalarials
Influenza[3]
Influenza, poliomyelitis
Supranational reference laboratory for tuberculosis
Arboviruses, viral respiratory infections including influenza[3], *hantaviruses*
Influenza, poliomyelitis, measles, rubella
Influenza and respiratory viruses, HIV, poliomyelitis, rabies, measles, tuberculosis, leishmaniasis, toxoplasmosis, mycosis and antifungals, antibiotic resistance, bacterial meningitis, anaerobic bacteria and botulism, listeria
Human rabies, emerging and highly pathogenic viruses, viral hemorrhagic fevers (Ebola, Marburg, Lassa, CCHF, RVF, Yellow fever, Dengue), respiratory viruses (avian influenza, MERS-CoV, SARS), arboviruses (Zika, Chikungunya, WNV).
Arboviruses and hemorrhagic fevers, diphtheria, *Bordetella pertussis, Escherichia coli,* rabies, protein chemistry, prenatal diagnosis, national biochemistry, plague, Q fever, tularemia, malaria
Salmonellosis, shigella, *Vibrio cholerae*
Enterobacteria, influenza, viral hepatitis, leptospirosis, schistosomiasis, taxonomy of triatomines, rickettsiae, Zika virus, chikungunya, dengue, yellow fever, anthrax, onchocerciasis, mansonellosis, Simuliidae, echinococcosis, poliomyelitis and other enteroviruses, malaria, hematozoan vectors, viral gastroenteritis, rotavirus, AIDS and endemic co-infections, leishmaniasis, systemic mycosis, tuberculosis, Chagas disease, histopathological anatomy, parasitology, pathological anatomy, plague, filariasis, *hantaviruses* and *arboviruses*

Prevent

Despite significant progress, the prevention, surveillance and control of infectious diseases remains a major challenge, particularly where health systems are weak. In a context of globalization, increasing urbanization, climate change, conflicts and migration, this fight must be international and involves the Institut Pasteur International Network.

"The Institut Pasteur International Network has consistently proven its engagement with WHO, OIE, FAO and countries to strengthen surveillance, laboratory capacities and early warning systems. With its wide variety of capacities, including reference laboratories and collaborating centres, at national, regional and global levels, and through collaborations with WHO and the Global Outbreak Alert and Response Network (GOARN), it contributes to the rapid detection and better understanding of pathogen emergence. It also advances R&D for diagnostics, vaccines and therapies, enabling the prevention, surveillance, and control of infections. The Network is therefore extremely well placed to partner with WHO for the implementation of its 13th General Programme of Work and its "3 billion programme", in order to address the public health challenges facing us."

DR. SOUMYA SWAMINATHAN,
Chief Scientist, WHO

A *one health* approach **for effectively detecting vector-borne diseases**

Faced with the increase in infectious risks common to humans and animals, the adoption of a systematic, integrated approach to health has become inevitable to preserve it. The MediLabSecure project, supported by the European Commission and coordinated by the Institut Pasteur, is part of this *one health* dynamic in the Mediterranean and Black Sea. It requires the mobilization of experts in human health, animal health and the environment to best prepare for health threats.

The geographical continuity between countries in the Mediterranean and Black Sea region, and the movement of people, animals and goods have consequences for public health which must be dealt with by these countries in an adequate, coordinated way. Faced with this increased risk of emerging viruses, it is essential to reinforce the capacities of laboratories and public health institutions in the region in order to rapidly and effectively detect viral infections. This is the objective of the MediLabSecure project which, through the training and connecting of international experts, aims to improve the preparation of teams in the face of vector-borne viruses (arboviruses).

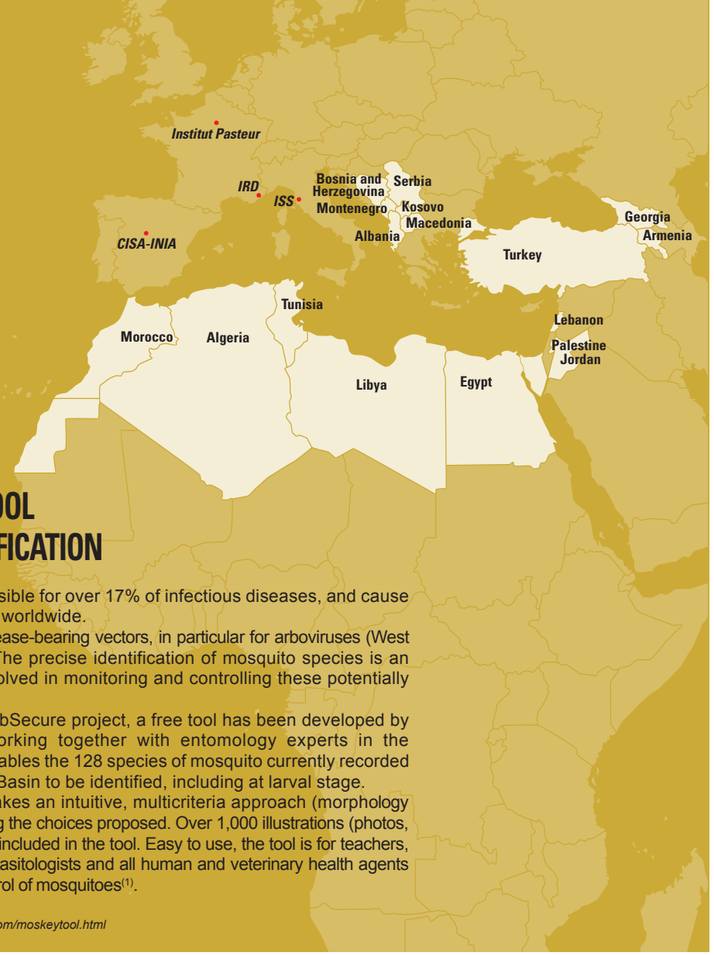
The MediLabSecure project, coordinated by the Institut Pasteur, is implemented by four European partner institutions: the Instituto Nacional de Tecnologia Agraria y Alimentaria (INIA), the Institut Pasteur, the Institut de recherche pour le développement (IRD) and the Italian National Institute for Health (ISS). Over the last four years, the teams involved have established a unique multidisciplinary network across 19 countries that are not part of the European Union in order to promote the integrated surveillance of emerging arboviruses through a *one health* approach.

Multidisciplinary interactions within the network between human and veterinary virologists, entomologists and public health contacts promote the response to emerging viral threats. The network has grown successfully since its launch in 2014. Today, over 60 laboratories and public health institutions have joined the network, and 560 participants from the countries involved have been trained at 13 technical workshops, with 8 taking place in 2017-2018. In total, 15 networking meetings have been organized, 9 scientific articles have been published (3 of which in 2017-2018) and several tools for reinforcing the *one health* surveillance of arbovirus infections have been developed *(including MosKeyTool, see box)*.

The MediLabSecure project, with its dynamic, multidisciplinary network, reinforces health security through the sharing of knowledge and experience, the strengthening of capacities and networking. Originally located in the Mediterranean and Black Sea region, the project continues to develop, adding to its network five Sahel countries – Burkina Faso, Mauritania, Mali, and Niger and Senegal through the inclusion of the Institut Pasteur de Dakar and CERMES, both members of the Institut Pasteur International Network.

MEDILABSECURE
is supported for an additional three years (until 2021) by the European Commission.

MediLabSecure



MOSKEYTOOL : A FREE INTERACTIVE TOOL FOR MOSQUITO IDENTIFICATION

Vector-borne diseases are responsible for over 17% of infectious diseases, and cause over one million deaths each year worldwide.
Mosquitoes are one of the main disease-bearing vectors, in particular for arboviruses (West Nile virus, Rift Valley virus, etc.). The precise identification of mosquito species is an essential step for laboratories involved in monitoring and controlling these potentially epidemic diseases.
Under the auspices of the MediLabSecure project, a free tool has been developed by an IRD team in Montpellier, working together with entomology experts in the MediLabSecure network, which enables the 128 species of mosquito currently recorded in Europe and the Mediterranean Basin to be identified, including at larval stage.
Identification using MosKeyTool takes an intuitive, multicriteria approach (morphology and distribution characteristics), using the choices proposed. Over 1,000 illustrations (photos, diagrams and distribution maps) are included in the tool. Easy to use, the tool is for teachers, students, medical entomologists, parasitologists and all human and veterinary health agents tasked with the surveillance and control of mosquitoes[1].

1 More information: https://www.medilabsecure.com/moskeytool.html

DETECT: predicting epidemics with satellite images

In Cayenne, Claude Flamand, head of the epidemiology unit at the Institut Pasteur de la Guyane (Pasteur International Talent Award 2018), has been collaborating with the National Center for Space Studies (CNES) since 2014 on an innovative project entitled DETECT, to target high-risk zones and predict a Dengue epidemic several months before it happens. The method consists of using satellite images to characterize the environment at a very small scale: *"Thanks to very high definition images, we can identify residential areas around which we can observe vegetation, lots of fruit trees or plants, a swimming pool etc. Entomologists then collect mosquitoes and larva on the ground. By cross-referencing the environmental data gathered by satellite with on-the-ground data, we are attempting to obtain models that can be extrapolated to all residential areas."* Once validated, this method will provide a very useful map for those involved in the anti-vector fight, enabling them to prioritize high-risk areas for mosquito control. The DETECT project is scheduled to end in 2019. *"The combination of all these spatial, climatic, environmental, sociobehavioral and immunological data could, in the future, tell us where an epidemic will take place and which population will be affected,"* summarizes Claude Flamand. This research could therefore lead to the implementation of concrete actions for the health of local populations.

Organizing monitoring
and early warning systems

The need to strengthen countries' abilities to face epidemic outbreaks became clear following the SARS epidemic and the revision of the International Health Regulations (IHR), long before the Ebola epidemic in West Africa. Since 2006, three cooperation agreements have therefore been signed by the Institut Pasteur International Network and the Assistant Secretary for Preparedness and Response (ASPR), under the American Department of Health and Human Services (DHHS). The ASIDE (Alerting and Surveillance for Infectious Disease Epidemics) project represents the third facet of this long-term collaboration. Its objective is to help countries to develop and maintain their public health capacities and train teams at a national level to prepare for and respond to epidemics of influenza and other potentially epidemic pathogens.

Implemented by the members of the Institut Pasteur International Network in Senegal, Ivory Coast, Cameroon, Central African Republic, Madagascar and Cambodia, the ASIDE project is coordinated by the Institut Pasteur Department of International Affairs.

In 2017 and 2018, this project supported the response to the epidemics of Ebola virus (2014), Dengue in the Ivory Coast (2017), plague in Madagascar (2017) and monkeypox in the Central African Republic and Cameroon (2018). This has enabled several epidemic outbreaks to be identified rapidly thanks to the surveillance systems used. Furthermore, the project has contributed to investigations into epidemics via the intervention of experts from partner institutions, the training of local staff and the purchasing of materials.

The particularly flexible program adapts to the local priorities of each country. In Cambodia, for example, activities focus on monitoring the circulation of the avian influenza virus within live poultry markets and investigating their supply chain in order to evaluate the circulation of the avian influenza virus in the country[1]. Given the success of this long-term collaboration between the Institut Pasteur International Network and the DHHS, the cooperation agreement will be extended by 5 years through the Pasteur International Network association.

Since 2017, experts from the Network, supported by the American Center for Disease Control and Prevention (CDC) through the shared agreement, have been steering a training program for laboratory technicians for eleven French-speaking African countries. This program aims to reinforce their capacities for the laboratory-based detection of respiratory viruses other than influenza and acute bacterial meningitis. Targeting the specific needs of the countries in question, it includes several training opportunities and internships at the Institut Pasteur, as well as workshops and visits for implementation and follow-up on site.

1 https://www.pasteur.fr/fr/institut-pasteur/institut-pasteur-monde/actualites/grippe-aviaire-marches-cambodgiens-haute-surveillance

LAUNCHED 12 YEARS AGO, THE ASIDE PROJECT HAS CONTRIBUTED TO:

- The implementation of national influenza surveillance networks bringing together primary care centers and hospitals.
- The gradual extension of the surveillance network to different geographical zones.
- The synchronization of syndromic and biological surveillance for identifying circulating pathogens.
- The harmonization of diagnostic methods across different countries.
- Training of laboratory staff and public health authorities on the IHR (2005).
- The extension of surveillance from influenza and respiratory pathogens to other febrile syndromes such as malaria and arboviruses.
- The collection of real-time surveillance data thanks to SMS transmission of epidemiological information, which can then be used to detect and predict public health events and for the rapid sharing of information with public health authorities to facilitate decision-making.

Emmanuel Nakouné Yandoko

Scientific Director of the Institut Pasteur de Bangui

Does monkeypox represent a future threat?

Monkeypox was clinically reported in the Central African Republic (CAR) for the first time in 1984. It wasn't until 2001 that this disease was confirmed by the Institut Pasteur de Bangui, thus allowing the technical equipment to be reinforced to carry out virological surveillance and monitor the level of circulation of the virus in the human population and its reservoir. The disease, characterized by a skin rash and fever, is fatal in 1 to 10% of cases. Faced with the increased frequency observed in the CAR over recent decades, the Ministry of Public Health entrusted the coordination of the Surveillance and Laboratory *Task Force* to the Institut Pasteur de Bangui, which is home to the WHO National Reference Center for arboviruses, hemorrhagic fever viruses, emerging viruses and zoonoses, responsible for the surveillance of monkeypox epidemics.

What warning system has been implemented by the Institut Pasteur de Bangui for monitoring monkeypox epidemics?

In this context, we established a monkeypox surveillance network with Doctor Without Borders (DNB known as MSF) across the health regions in the CAR.
The system implemented confirmed 12 micro-epidemics between 2001 and 2018, occurring more and more frequently from 2015. A case definition, approved by WHO and the Ministry of Health, has been included in all health training, in addition to sociodemographic and clinical information, and images of the typical skin rash that could suggest a monkeypox infection. An epidemiological and reservoir investigation is carried out for each confirmed case. This provides important information on potential reservoirs for this emerging disease since the eradication of smallpox in 1980.

How can we improve our knowledge of this disease?

In order to position the Institut Pasteur International Network in the fight against this emerging disease, the Institut Pasteur de Bangui, the Institut Pasteur and the National Natural History Museum are leading a cross-functional research project entitled "Afripox: studying monkeypox in the *one health* concept: human infection, animal reservoir, disease ecology and diagnostic tools[1]". The goal is to understand monkeypox at the human-animal interface. This project aims to improve knowledge of the perception rural populations have of this disease, its reservoir and risk factors for zoonotic and interhuman transmission. It will lead to the development and implementation of preventive and diagnostic tools on the ground, with most cases occurring in regions that are difficult to access.
In the case of the CAR, the majority of cases have occurred in the south of the country, characterized by a forest ecosystem that is favorable to the emergence of these pathogens.
The project will provide a better understanding of circulating strains and the role of ecological factors in the emergence of monkeypox in central Africa.

1 Epidemiology: Arnaud Fontanet; Virology: Jean-Claude Manuguerra, Antoine Gessain and Emmanuel Nakoune; Anthropology: Giles Tamara and the National Natural History Museum: Alexandre Hassanin.

Concrete actions: **the first Institut Pasteur de Guinée laboratory**

In response to the wishes expressed by Guinean authorities following the Ebola crisis, on September 21, 2015, the Institut Pasteur and the Republic of Guinea signed a Memorandum of Understanding regarding the creation and running of the Institut Pasteur de Guinée in Conakry, 32nd member of the Institut Pasteur International Network. The objective of the Institut Pasteur in Guinea, led by Dr. Noël Tordo, is to respond to epidemic emergencies, participate in infectious diseases surveillance and research, and to train and support Guinean scientists in the prevention of infections. It inaugurated its first laboratory on October 22, 2018.

The Gamal Abdel Nasser University of Conakry (UGANC) has provided the Institut Pasteur de Guinée with 230 m^2 of space to enable it to begin its work as quickly as possible. This space has been renovated to house a modern training center, the Pasteur Laboratory, thanks to the support of the French Ministry of Europe and Foreign Affairs (MEAE) and Expertise France (LABNET project). The Pasteur Laboratory is dedicated to training, diagnostics and research. The training offered covers various topics: serological and molecular diagnostics, good laboratory practice, biosecurity etc.

The Institut Pasteur de Guinée will initially focus on potentially epidemic diseases, in particular arboviruses and hemorrhagic fever viruses of zoonotic origin in a *one health* approach, with the creation of a first virology unit. The Institut Pasteur de Guinée hopes to reinforce Guinean research by developing collaborations with other national research structures and contributing to the training of future generations of Guinean scientists. The institute is also building a biobank, primarily microbiological, which is open internationally, in particular through the global connected biobanks project within the Institut Pasteur International Network *(Pasteur Institute Bioresources network* – PIBnet).

Initial research activities are focused on the role domestic and wild animals may have played in the transmission of the Ebola virus. These activities are the result of numerous scientific collaborations, in particular with the Friedrich Loeffler Institute ("Ebola-Foresight" project financed by the German Ministry of Agriculture) and the World Organization for Animal Health (OIE), the French Agricultural Research Center for International Development (CIRAD) and the Institute for Research for Development (IRD) ("EBO-Sursy" project financed by the European Union). These research activities are accompanied by reinforced capacities at a regional level (Guinea, Sierra Leone).

SUPPORT FOR THE INSTITUT PASTEUR DE GUINÉE

- **French Development Agency (AFD)**
- **French Ministry of Europe and Foreign Affairs (MEAE) (LABNET project)**
- **Republic of Guinea**

CONSTRUCTING THE INSTITUT PASTEUR DE GUINÉE – LOOKING FORWARD TO 2020

The next step will be the creation of the permanent building, financed by the AFD, on a plot of land generously provided by the Republic of Guinea in the heart of the city of Conakry. Construction will begin in September 2019, with completion expected in late 2020. With a surface of over 1,000 m^2, the Institut Pasteur de Guinée will have a wing of laboratories (biobank, P1, P2 and P3), a wing specifically for administrative offices, and a meeting room.

Ousmane Faye

Director of the virology department, Institut Pasteur de Dakar

How do we react to emerging epidemics?

I was deployed to Guinea (2014-2016) to supervise the Ebola virus diagnosis laboratory which was entrusted to the Institut Pasteur de Dakar. I was involved on the ground as part of the fight against the 10th Ebola epidemic, which emerged in North Kivu, in the Democratic Republic of Congo (DRC). To respond to an emerging epidemic that that of the Ebola virus, several teams are involved in monitoring and identifying cases, providing care, communication and prevention. The laboratory plays a central role as it confirms all cases in order to guide the response.
The Institut Pasteur de Dakar WHO collaborating center (WHOCC) teams on the ground support the national laboratories of the countries experiencing the epidemic. As the conditions on the ground are often difficult in the majority of African countries, easy-to-use, pre-evaluated diagnostic tools must be available.

How is the mobilization organized?

The WHOCC provides a team of laboratory technicians who are experts in using diagnostic tools and senior scientists for validating results. Interactions with other key actors in the response, clinicians and epidemiologists, are necessary for the correct analysis and interpretation of the results. The patient's origin, contact with confirmed cases, vaccination status, clinical signs at time of admission, date of onset of symptoms and the patient's status at the time samples are taken are all important information to be recorded on an "investigation form". The WHOCC has multiple roles, but diagnosis is one of the essential elements in the management of an epidemic like that of Ebola. Beyond surveillance, it would be dangerous to miss the diagnosis of an infected patient, who would then be in contact with the population, or hospitalize a patient without the infection with confirmed cases and thus expose that patient to the disease.
The communication team is in charge of informing the population, as a critical element for controlling the epidemic is interrupting the chain of transmission.

Can you see differences between the Ebola epidemics in Guinea and in the DRC?

The Ebola epidemic in Guinea started in the south east in December 2013, before spreading to Liberia and Sierra Leone, and affected at least 28,000 cases with over 11,000 deaths. It was the first time that this virus, for which there is no known treatment, led to contamination outside of central Africa, and then outside the African continent.
The epidemic ongoing in the DRC, which WHO has labeled a "global heath crisis", is the tenth declared in the country since the appearance of this disease on Congolese soil in 1976.
The epidemic in West Africa took place in a context where the countries had no experience in managing the disease and were not prepared to respond to an Ebola epidemic. The DRC has prepared teams, easy-to-use diagnostic tools and promising treatments than can be used. The instability of the province of North Kivu is the main obstacle to the fight against the epidemic.

A better understanding of epidemics:
the 2017 outbreak of pneumonic plague in Madagascar

Plague is an endemic disease in Madagascar. Each year, it presents a seasonal upsurge between the months of September and April, particularly in the central highlands situated at an altitude of over 800 m. In 2017, an unprecedented epidemic of pneumonic plague hit the island, mainly affecting the capital Antananarivo and Toamasina, the island's main port. Researchers from the Institut Pasteur de Madagascar and the Institut Pasteur in Paris, in collaboration with the Malagasy Ministry of Public Health, the World Health Organization and international experts, described the extent of the 2017 epidemic of pneumonic plague in Madagascar and the dynamics of its transmission.

Plague, thought of as a disease of the past in other countries, is an endemic disease in Madagascar, which declares 75% of global cases of plague reported to WHO. Every year, Madagascar records 200 to 700 suspected clinical cases, mainly of bubonic plague. A zoonosis affecting the rural central highlands at an altitude of over 800 m in particular, each year it presents a seasonal upsurge between the months of September and April. Between August and November 2017, an urban epidemic of pneumonic plague was declared.

At the origin of this epidemic was a patient who died from respiratory distress during a bush taxi ride between the central highlands and the port of Toamasina on the east coast of the country. This epidemic was unusual due to its extent (almost 2,500 declared or suspected cases), the date at which it started and its geographical distribution, mainly affecting two cities; the capital Antananarivo and the port city of Toamasina.

Under the Malagasy National Anti-Plague Program, all suspected clinical cases of plague must be declared to the Ministry of Public Health Central Plague Laboratory (LCP, housed within the Institut Pasteur de Madagascar, Antananarivo), where all clinical and epidemiological information is recorded. Confirmation of suspected cases of plague using biological analysis is also carried out here. Using cases reported from August 1 to November 26, 2017 (official end of the pneumonic plague epidemic), epidemiological and sociodemographic information, clinical characteristics and fatality were estimated by researchers at the Institut Pasteur de Madagascar and the Institut Pasteur in Paris and their collaborators. During this predominantly urban epidemic, 2,414 suspected clinical cases were declared, one quarter of which were categorized as confirmed or probable cases of plague.

Analysis showed a predominance of pneumonic cases, representing 78% of the 2,414 notified cases, with the number of confirmed (with culture) or probable (with molecular diagnostics or a rapid diagnostic test) cases of pneumonic plague doubling on average every five days after the initial phase of the epidemic. The results of this study have been published[1].

The fatality rate was higher in confirmed cases of pneumonic plague (25%) and bubonic plague (24%) than in probable or suspected cases. Antananarivo, the capital, and Toamasina, the island's main port, were most affected by this epidemic of pneumonic plague.

The country had not faced an epidemic of this scale in twenty years. Several challenges arose, concerning not only the country's health authorities response to the outbreak and the activities of the Central Plague Laboratory, but also the management and analysis of epidemiological data by the teams at the Institut Pasteur de Madagascar.

This epidemic highlighted the risks of pneumonic plague reappearing and spreading rapidly in urban areas. The lessons learned from this epidemic will be key to improving future investigations and responses to epidemics in Madagascar and elsewhere.

This work was supported by the Institut Pasteur Department of International Affairs through the ASIDE project and its collaboration with the American DHHS.

1 Epidemiological characteristics of an urban plague epidemic in Madagascar, August–November, 2017: an outbreak report. *Randremanana R, Andrianaivoarimanana V, Nikolay B., et al.* Lancet Infectious Diseases, *mars 2019. Doi:10.1016/S1473-3099(18)30730-8.*

An innovative tool for investigating epidemics:
closer to the source with the mobile laboratory

This truck, owned by the Institut Pasteur de Dakar since 2018 thanks to a collaboration with the Praesens Foundation, is fully equipped, autonomous and easy to deploy. By moving the reference laboratory closer to where an epidemic is taking place, it is possible to provide rapid access to molecular diagnostics, even in isolated areas, and reliable results in real time, which are essential for the rapid care of patients and controlling the disease. The objective of this project is to evaluate the laboratory truck in terms of mobility, robustness, self-sufficiency for energy, the functioning of the integrated equipment (isolator, Idylla diagnostic instruments, etc.), and the rapidity and reliability of diagnostic results.

Is it possible
to predict epidemics?

The Institut Pasteur in Paris and five members of the Network in sub-Saharan Africa[1] are part of the ALERRT (African coaLition for Epidemic Research, Response and Training) network. The ALERRT network, founded by a European & Developing Countries Clinical Trials Partnership (EDCTP), promotes clinical research on epidemics and institutes work with it to plan the future.

1 Institut Pasteur de Madagascar, Institut Pasteur de Côte d'Ivoire, Pasteur Center in Cameroon, Institut Pasteur de Dakar, Institut Pasteur de Bangui.

Alert

The Network's scientific expertise is crucial for responding to the challenges posed by resistance. For example, the emergence of pathogens resistant to numerous molecules means that scientific, health, environmental, political, industrial and social obstacles must be overcome.

"Despite the progress made and the unending efforts of clinicians and scientists, antimicrobial resistance has become one of the most serious threats to health around the world. The one health *approach is needed to develop effective, sustainable solutions, in particular new drugs, vaccines, better diagnostics and technologies that meet health, veterinary, agricultural and environmental needs. The Network, with its 32 members across the world, has proven its expertise and leadership in the face of this alarming situation. Its last symposium highlighted the importance of international collaborations in research, bringing together researchers, clinicians and health experts."*

PROF. KEIJI FUKUDA,
Director and Clinical Professor
School of Public Health, Li Ka Shing Faculty of Medicine
The University of Hong Kong, Hong Kong, China

The Institut Pasteur International Network against resistance

The Institut Pasteur International Network dedicated its 4th scientific symposium to resistance. Entitled *"Combating Resistance: microbes and vectors"*, this high-level meeting on November 15 and 16, 2018, brought together almost 400 scientists from across the world for presentations on cutting edge research.

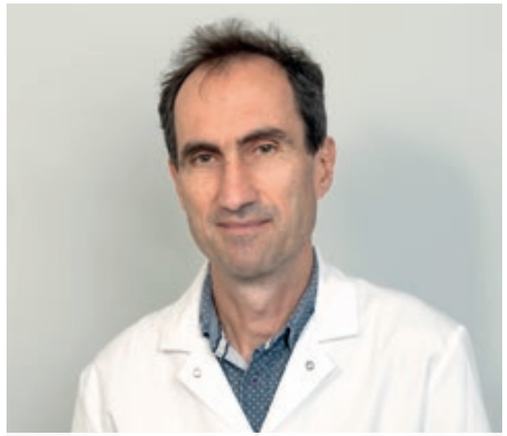
Alexander Fleming himself, the inventor of penicillin, was already aware of the threat that bacterial resistance to antibiotics could represent. But today, this threat has become particularly worrying: we estimate that 700,000 deaths around the world each year are due to resistance to treatment during infection. And if effective anti-resistance strategies are not put in place, this figure could reach 10 million in 2050, according to a report published in 2016 by Lord O'Neill, the former Commercial Secretary to the British Treasury.

Antibiotic resistance surveillance data published by the World Health Organization (Global Antimicrobial Resistance Surveillance System – GLASS) reveals high levels of resistance to a number of serious bacterial infections in both high- and low-income countries. The most commonly reported resistant bacteria were *Escherichia coli*, *Klebsiella pneumoniae, Staphylococcus aureus, Neisseria gonorrhoeae* and *Streptococcus pneumoniae, followed by Salmonella spp*[1].

The symposium highlighted the diversity of the work carried out within the Network on all pathogenic microorganisms, but also on their vectors, both insect and animal, and avenues that should be explored for improving diagnostic and surveillance tools and developing innovative treatment strategies. Above all, it enabled teams to get to know each other and think about future transnational and multidisciplinary collaborations. One of the topics proposed under the call for applications for future Institut Pasteur Cross-Functional Research Programs relates to antibiotic resistance.

This event also provided the occasion to present the Robert Deschiens Prize to Dr. Moritoshi Iwagami from the Institut Pasteur du Laos. Prof. Yves Buisson, president of the French Exotic Pathology Society, awarded him the prize, which rewards his work on the artemisinin resistance of *Plasmodium falciparum* as well as his commitment to the training of young Laotian scientists in parasitology[2].

1 Extracts from the WHO press release of January 29, 2018: https://www.who.int/mediacentre/news/releases/2018/antibiotic-resistance-found/fr/
2 https://www.pasteur.fr/en/home/research-journal/news/high-level-international-conference-microbes-and-vectors-resistance



Philippe Glaser

Head of the Ecology and Evolution of Antibiotics Resistance Unit, Institut Pasteur

How do we explain the phenomenon of antibiotic resistance?

To answer this question, it is first necessary to understand what antibiotics really are: molecules that enable bacteria to be killed within the human body, without affecting human cells. Antibiotics have become indispensable to the treatment of a large number of pathologies. However, these molecules are, for the large majority, produced by... bacteria. These bacteria protect themselves against the effect of the antibiotics they produce thanks to genes that code for resistance functions. These genes can be transmitted and pass from one bacteria to another. Furthermore, bacteria can undergo genetic mutations and thus acquire resistance "capacities". The resistance of bacteria to antibiotics is therefore a phenomenon that is inherent to the very existence of antibiotics.

However, this phenomenon is developing...

Bacteria are extremely numerous and multiply very quickly. If a single one escapes a treatment, it can very rapidly repopulate the environment that has been treated. And if it escapes a treatment because of resistance, it repopulates the environment with bacteria of the same species that are also resistant, and the treatment is no longer effective. Thus, very common bacteria like *Staphylococcus aureus* and *Escherichia coli* were previously sensitive to antibiotics but are today becoming multiresistant. So, while the problem of resistance existed from the time when antibiotics were discovered, the phenomenon has grown with their increased, sometimes unsuitable, consumption, particularly over the last ten years. This is attributable to a number of causes, including the underdosing of poor quality antibiotics, the massive use of antibiotics in some intensive livestock farming, potentially their discharge into the environment, and the transmission of multiresistant bacteria between animals and humans. Poverty is also a factor, as it combines various causes. Furthermore, multiresistant bacteria can circulate across continents. Today, the situation is very serious in South East Asia (China, India, Cambodia, etc.). However, it should be noted that resistance is declining in some countries, where people have become aware of the phenomenon and reasonable use of antibiotics has been promoted.

What can be done to combat resistance?

Mainly two things. The first is to control the consumption of antibiotics. If bacteria are less exposed to them, there will no longer be natural selection on the basis of their resistance, and the proportion of non-resistance bacteria will grow. As a result, resistance will decrease.
In France, where more antibiotics are consumed than in Nordic countries, resistance has a real cost in terms of healthcare spending.
The second means consists of improving hygiene, in the everyday environment for developing countries and in hospitals for developed ones. In the hospital setting, one of the biggest challenges is rapidly detecting the presence of multiresistant bacteria in patients so that they can be isolated, if necessary, to avoid the bacteria spreading.

Circumventing viral disease
vector insecticide resistance

To curb endemic and epidemic viral diseases, a true scourge in several regions of the world, it is essential to control their vectors, generally insects, to stop them proliferating. However, several species have adapted to develop resistance to the molecules used. Several Network institutes are working to study this phenomenon and develop alternative strategies.
A significant share of the research efforts are naturally focused on mosquitoes, a vector of viral diseases and the leading animal cause of human mortality.

SURVEILLANCE OF RESISTANT MOSQUITO POPULATIONS

Chikungunya, dengue, Zika... These viral diseases, which are dangerous to man, are transmitted by different species of mosquito. In the absence of effective vaccines (with the exception of yellow fever and Japanese encephalitis) and/or specific treatments, the fight against these diseases relies on the control, often using chemicals, of the vectors that transmit them. In addition, local populations are encouraged to wash away larval populations. These strategies aim to limit the density of mosquitoes, which is associated with a higher risk of transmission of arboviruses.

However, the large-scale use of insecticides results in the adaptation of insect populations to these molecules and thus a loss in their efficacy.

This is the case of the *Aedes aegypti,* a vector of dengue and other arboviruses in particular. One example of a molecule used at a global scale against adult mosquitoes is deltamethrin, a pyrethroid marketed for the last twenty years and widely used in public health and agriculture due to its low toxicity to humans. In a context of strong resistance in the majority of French overseas territories, the REAGIR[1] project financed by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) has continued the collaboration between the Institut Pasteur de la Guyane and that in New Caledonia. Its main objective was to provide a better understanding of the evolution of pyrethroid resistance and its mechanisms within populations of *Aedes aegypti*. Populations from French Guiana proved much more resistant to deltamethrin than those from New Caledonia. Molecular markers of resistance show an almost fixed level of resistance de la Guyane. At the Institut Pasteur de la Guadeloupe, an investigation of *Aedes aegypti* and *Culex quinquefasciatus* mosquitoes showed that the two species have developed significant resistance to several insecticides, with several mechanisms of resistance identified. Furthermore, a Inter-Pasteurian Concerted Action led by the Institut Pasteur de Bangui in association with the institutes in Madagascar and French Guiana studied the resistance of *Aedes albopictus* and *Aedes aegypti* in order to look for molecular mechanisms and identify reliable early markers for surveillance.

The results are clear: across the world, widely used insecticides are less and less effective. In this context, it is crucial that a review of the situation is carried out and regular surveillance implemented in order to establish resistance management strategies and alternative methods for fighting mosquitoes.

MANAGING RESISTANCE IN LAOS AND CAMBODIA

Laos and Cambodia are regularly hit by epidemics of dengue. The authorities in these two countries do not sit idly by. The actions they implement, consisting of the spreading of large quantities of pyrethroid-based larvicides, have so far proven to be harmful and above all ineffective – and for a reason! The Institut Pasteur du Laos and the Institut Pasteur du Cambodge have both shown that all mosquitoes have become resistant to the insecticides used in this fight. Laos[2] has reacted quickly to the recommendations given by the institutes, banning temefos and replacing it with a biological insecticide, *Bacillus thuringiensis* var. *israelensis* (BTI), which is already used around the world and to which mosquitoes are not resistant. The two institutes work together on the issue of vector insects on a regular basis. They are partners of the second facet of the ECOMORE (ECOnomic Development, ECOsystem MOdifications, & Emerging Infectious Diseases Risk Evaluation) project, financed until 2020 by the French Development Agency (AFD).

ALTERNATIVE STRATEGIES UNDER THE MICROSCOPE

Among the alternatives to insecticides, one of the most promising strategies, tested in New Caledonia, is *"Wolbachia"*[3]. This is a bacteria with particularly interesting properties: although *Aedes aegypti* does not naturally contain the bacteria, when the mosquito is artificially inoculated with *Wolbachia*, the bacteria establishes itself and is passed on to the mosquito's descendants. Above all, the bacteria slows down viral multiplication within the mosquito, making it unable to transmit the virus when it stings. Releasing the infected mosquitoes into nature leads to the diffusion of the bacteria in populations of *Aedes aegypti*, thus preventing the transmission of dengue.

At the Institut Pasteur de la Guadeloupe, research into alternative methods aims to identify the pheromones of the *Aedes aegypti* mosquito. The objective of this is to establish mosquito attraction/repulsion devices in order to reduce human-vector contact or create sexual confusion to prevent mating. An initial cartography of the odors emitted by the *Aedes aegypti* mosquito throughout its development was carried out in 2016-2018[4].

1 With LECA (Grenoble) and the IRD (Montpellier). Dusfour I. Résistance aux pyréthrinoïdes chez Aedes aegypti: évaluation de nouveaux candidats insecticides et étude du phénomène de réversion. Les Cahiers de la recherche. Santé, Environnement, Travail, ANSES, 2017.
2 Alternative insecticides for larval control of the dengue vector Aedes aegypti in Lao PDR: insecticide resistance and semi-field trial study. *Marcombe S et al.* Parasit Vectors, *December 2018. Doi: 10.1186/s13071-018-3187-8.*
3 With Monash University, the New Caledonia Department of Health and Social Affairs and Noumea City Hall: www.eliminatedengue.com
4 With the Shandong Academy of Agricultural Sciences, China. Cartography of Odor Chemicals in the Dengue Vector Mosquito (Aedes aegypti L., Diptera/Culicidae). *Wang F. et al.* Scientific Reports, *11 juin 2019. Doi:10.1038/s41598-019-44851-7.*

Understanding and fighting pediatric **antibiotic resistance**

Antibiotic resistance is especially concerning in low income countries, as the prescription and consumption of these molecules is not regulated. The two major "reservoirs" of resistance are hospitals and the daily environment - in other words where people live, the community. However, there are very few data on community antibiotic resistance, despite the fact that these data are essential for the implementation of an effective strategy for fighting this phenomenon. This is particularly the case as in low income countries, the hospital is generally a last resort due to the cost for local people.

UPDATE TO WHO RECOMMENDATIONS NEEDED

The World Health Organization (WHO) recommends the use of two antibiotics for combating neonatal infections. However, the BIRDY project has shown that two-thirds of bacteria responsible for these infections are responsible to at least one of the two antibiotics in the regions covered by the study. WHO must therefore update its recommendations. However, this is not simple: in the face of resistant, or multiresistant, bacteria, it is often necessary to use expensive antibiotics that are unattainable in low income countries.

The Institut Pasteur has established the **BIRDY** *(Bacterial Infections and antibiotic Resistant Diseases among Young children in low-income countries)* project, which took place from 2012 to 2017 in Madagascar, 2014 to 2018 in Cambodia, and 2014 to 2019 in Senegal, in order to study antibiotic-resistant infections in neonates (during the first month of life).

In total, 3,834 mother-child couples participated in the project: 814 in Cambodia, 750 in Senegal and 2,270 in Madagascar. The mothers who participated were recruited and monitored before birth so that the Institut Pasteur teams could examine their babies as soon as they were born. Visits took place twice per week and samples were taken as soon as a pathology was identified.
Although the results of the studies in Cambodia and Senegal have not yet been published, the BIRDY project has revealed initial results from Madagascar, where figures from the pilot phase have been published. A very high frequency of community bacterial neonatal infections was shown, with an incidence of 17.7 cases per 1,000 births. As a comparison, this rate is fewer than 1 for 10,000 in the United States and France.
In 75% of cases, the infection occurred in the first week of life. Public health policies could therefore target this crucial period in Madagascar, and undoubtedly more generally in low income countries.

"Our results highlight the importance of reinforcing monitoring and care in regard to childbirth at the community level. It is important to remember that over one third of the women in our cohort gave birth at home" explains Bich-Tram Huynh, researcher in the Pharmacoepidemiology and infectious diseases unit at the Institut Pasteur, and co-principal investigator for the BIRDY program.

Finally, the incidence of infections caused by multiresistant bacteria was 7.7 cases per 1,000.

"It is the first time that this rate has been estimated in the community. These relatively mitigated preliminary results compared with what we expected, if they are confirmed, indicate that there is still time to implement actions to limit the diffusion of these multiresistant bacteria in the community" notes Jean-Marc Collard, head of the Experimental bacteriology unit at the Institut Pasteur de Madagascar and co-principal investigator of the BIRDY program.

A second program (BIRDY 2) was already initiated in Madagascar in December 2018. This second phase remains focused on neonatal infections and antibiotic resistance, but extends to the study of animal and environmental reservoirs of resistance, and is accompanied by a facet for the documentation of cases of bacterial infection in premature children. This new program includes some aspects of the *one health* movement in its implementation.

RESISTANT BACTERIA TRANSMITTED BY FOOD?

As part of BIRDY in Cambodia, researchers at the Institut Pasteur have compared resistant bacteria found in meat and fish samples from two markets in Phnom Penh to those that contaminated pregnant women living close to the markets and infected patients in Sihanouk Hospital Center of Hope. A large proportion of the bacteria from human subjects were genetically similar to those found in food, and were notably resistant to an antibiotic only administered to animals. This strongly suggests that these resistant, potentially pathogenic bacteria could be transferred in food.

BIRDY
is supported in Madagascar by the Principality of Monaco, in Senegal by the Total Foundation and in Cambodia by MSDAVENIR.
The Institut Pasteur is the sponsor of the project.

Protect

The public health mission of the Institut Pasteur International Network, underpinned by high-level scientific activities and training, is at the heart of Pasteurian values. Faced with emerging diseases and vulnerabilities, the Network's scientists are committed to serving local populations to overcome public health challenges.

"The multiplication of human and animal exchanges significantly increases the health risks associated with the emergence of infectious diseases and indicates the need to reinforce international coordination and health security policies.
With over 2.5 million euros per year, French funding represented more than one quarter of the resources available to WHO headquarters for the implementation of the new International Health Regulations.
The mobilization of experts from the Institut Pasteur International Network is vital for the reinforcement of laboratory and biological risk prevention capacities in developing countries. The Network's actions encourage global health challenges to be taken into account for public decision-making.
All of the knowledge shared through the Network unquestionably contributes to the implementation of relevant public health activities, adapted to the risk situation in question and the various vulnerabilities of local populations when dealing with the ongoing major changes."

PROF. JÉRÔME SALOMON,
Director-General for Health, Ministry of Solidarity and Health, France
Member of the Institut Pasteur Board of Directors

Essential support for **laboratories monitoring pathogens**

In 2018, the RESER (Network for the study and surveillance of emerging pathogens) program, steered by the Institut Pasteur, was launched in the Institut Pasteur International Network. It aims to strengthen bacteriological reference and surveillance activities within the Network, in particular through training and above all the bringing together of teams of microbiologists from laboratories and National Reference Centers with epidemiologists working on the ground.

Seven institutes are involved in the pilot phase of the RESER program (2018-2019), financed by LabEx IBEID: the Pasteur Center in Cameroon, the Institut Pasteur de Côte d'Ivoire, the Institut Pasteur de Dakar, the Institut Pasteur de Guinée, the Institut Pasteur de Madagascar, the Institut Pasteur du Maroc and the Institut Pasteur de Tunis.

The national reference centers and laboratories provide expertise in the microbiology and pathology of infectious agents. They contribute to epidemiological surveillance through the maintaining of a network of laboratories and the characterization of pathogens. Their mission is also to alert public health authorities of any events that could pose a threat to the health of the population and provide scientific advice to health authorities.

The microbiological surveillance role of national reference centers and laboratories depends on the level of collaboration within the "medical laboratory – national reference center or laboratory – epidemio-surveillance" circuit, which can sometimes prove defective. However, surveillance must be carried out in close, continuous collaboration with interventional epidemiology teams who can then implement concrete actions. In this context, the RESER program has established three specific courses organized at the Institut Pasteur.

The first course, given over 6 days in November 2018, covered microbiological surveillance in public health. It brought together and connected directors from 12 national reference centers and medical biology laboratories in the Network with epidemiologists from each country. Experts from the field of public health (AP-HP, Epicentre-MSF, Institut Pasteur, WHO, the French network of National Reference Centers, French Public Health) also participated. An additional two-week internship at an Institut Pasteur national reference center was proposed to the directors. A second course (March 2019, 3 days), giving an introduction to bacteriological techniques for public health reference activities has also been put in place. Designed for senior research technicians and engineers, it is followed by a practical 4-week internship in a French national reference center. This will be completed with a third course in October 2019, focusing on emerging bacteria in Africa for medical biology laboratory managers from institutes in seven target countries.

The next step aims to make the program permanent and extend it to other countries/institutes in Africa, integrate new pathogens and develop research programs (antibiotic resistance, factors in emergence, etc.).

RESER, AN AMBITIOUS PROGRAM WITH THREE MAIN OBJECTIVES:

- The establishment of a bacteriology surveillance network in the target countries (Cameroon, Ivory Coast, Senegal, Guinea, Madagascar, Morocco, Tunisia).
- The reinforcing of microbiologist-epidemiologist relations.
- The reinforcing of reference laboratory capacities so that they can adapt to new diagnostic methods (Maldi-TOF), whole genome sequencing (WGS) and metagenomic techniques.

Frédérique Randrianirina

Department Head, Clinical Biology Center
Institut Pasteur de Madagascar

What types of analysis are carried out at the laboratory?

The Clinical Biology Center is a multipurpose medical analysis laboratory, accredited under ISO 15189 for general and specialized biochemistry and pre and post-analysis phases. Several types of analysis are carried out in the laboratory. General and specialized biochemical analyses are carried out using blood samples and show, for example, tumor or cardiac markers, hormones, etc. In microbiology, the studying of samples reveals the presence of bacteria, parasites, fungi and infectious agents. The study of blood and its pathologies is also carried out in the laboratory, including coagulation tests to measure how well blood clots. Anatomocytopathology is another example of an analysis that looks at tissues and cells in order to identify and study the anomalies associated with a disease.

What is the analysis laboratory's role in public health?

The laboratory and its sampling center can accommodate up to 700 patients per day. It is open 24/7. This availability means analyses can be carried out urgently and patients receive their results very quickly, just two hours after samples are taken. This service, even if it must be paid for, is a major factor in the improvement of patient care and thus the institute's public health mission. Our laboratory is home to two national reference centers: the Salmonella, shigella and cholera national reference center (in collaboration with the food hygiene and environment laboratory) and the National biological reference center for antibiotic resistance (in collaboration with the experimental bacteriology unit). National Reference Centers are laboratories with expertise in microbiology and monitoring centers for transmissible diseases which participate in fighting and controlling these diseases through the centralization of information on a national scale.

How do the laboratory's activities contribute to research projects, and how are they essential?

The laboratory supports research projects by carrying out the medical biology analyses requested as part of these projects. They need laboratory analysis results to then study a pathology and draw conclusions on it, in a specific population or environment, for example. Our laboratory has contributed to various international and local research projects, including BIRDY 1 and 2 on infections in young children, Afribiota on childhood malnutrition, TB kids on tuberculosis, a study into abortion complications in Madagascar, pediatric diarrhea and more. The laboratory's analysis service also contributes to the funding of new research and public health activities for the Institut.

Contributing to a global vaccination strategy to **eliminate rabies by 2030**

In 2015, an international effort was initiated by WHO/OIE/FAO/GARC (Global Alliance for Rabies Control) with the aim of eliminating dog-transmitted human rabies by 2030. Seventeen of the 32 Institut Pasteur International Network institutes are located in regions where rabies is endemic. Their capacities for research and application have led to significant progress in the fight against this viral zoonosis in recent years. The adaptation of the post-exposure vaccination protocol is a major example of the implementation of new strategies for controlling this disease with epidemiologists working in the field.

Rabies is a viral zoonosis that is always fatal once the first signs of the disease have appeared. The Institut Pasteur, which has just celebrated its 130th anniversary, was created following the success of the rabies vaccine, developed by Louis Pasteur and his team. However, rabies continues to be a major public health issue in developing countries, in particular in Africa and Asia where it causes at least 60,000 deaths per year, 40% of which are children. In Cambodia, where approximately 800 deaths are thought to be attributable to rabies each year, almost 600,000 serious bites are caused by dogs.

Almost all cases of rabies in humans are caused by a rabid dog bite: the fight against human rabies is above all a fight against rabies in dogs. The human antirabies vaccine prescribed after a suspicious bite (post-exposure vaccination) is the only means of preventing the propagation of the virus from the inoculation site to the central nervous system. It is also used as prophylaxis in people exposed through their job and recommended for travelers in endemic zones. The canine vaccine, when administered on a large scale, interrupts the circulation of the virus in the canine population.

These two approaches to vaccination have led to the elimination of dog-transmitted human rabies in a large part of Europe, the Americas and most developed countries, but they are still underused in Africa and Asia, mainly due to their cost, logistical difficulties and the lack of information among the local population.

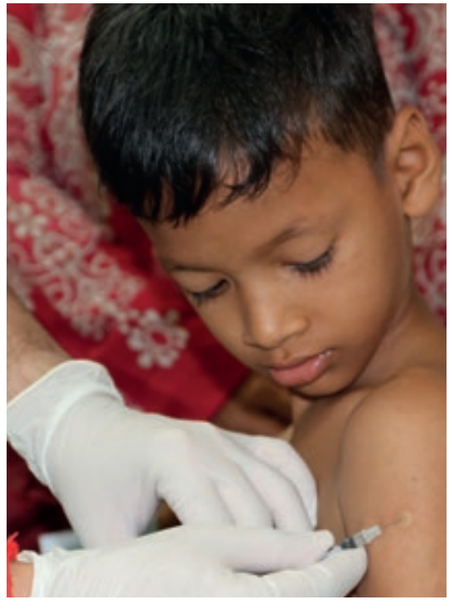
In April 2018, WHO published new recommendations on the use of antirabies vaccines and immunoglobulins as prophylaxis following exposure to the rabies virus, based on the research carried out over several years by teams at the Institut Pasteur du Cambodge in association with researchers from the Institut Pasteur in Paris.
Post-exposure vaccination by means of intradermal injection of reduced doses after wounds caused by animals (mainly dogs, but also pigs, cats, monkeys and bats) now takes place in 3 sessions (D0, D3, D7) over one week rather than 4 sessions over one month.

The significant shortening of the vaccination protocol, called the IPC protocol for the Institut Pasteur du Cambodge, improves patient management and access to care, particularly for patients from rural areas. The teams carried out a retrospective study of the clinical course of a large number of vaccinated patients. The researchers showed that there was no increased mortality in those who interrupted the protocol before the 4th injection[1]. Antirabies immunoglobulins remain necessary in addition to post-exposure prophylaxis in cases of serious bites in people who have not been previously vaccinated.

The IPC protocol is the first one-week post-exposure protocol recommended by WHO[2]. Its funding is therefore envisaged by the GAVI in 47 eligible countries from 2021. The Institut Pasteur du Cambodge, which accommodates almost 26,000 people bitten by a potentially rabid animal per year, remains committed to the fight against rabies, with the opening of its second vaccination center in Battambang in 2018 and its third in Kampong Cham in early 2019.

1 Tarantola A., Ly S., Chan M., In S., Peng Y., Hing C., et al. Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003-2014. Vaccine. *2018 Nov 16.*
2 https://www.who.int/rabies/resources/who_wer9316/en/

Essential epidemiological data
for adapting vaccination strategies Spotlight on whooping cough



Despite global vaccination coverage recommendations and the inclusion of the primary vaccination in WHO's Expanded Program on Immunization (EPI), whooping cough remains an endemic respiratory virus associated with significant morbidity and mortality, particularly in infants aged under 6 months. The primary whooping cough vaccination does not provide life-long immunity. The implementation of epidemiological surveillance is necessary for adapting national vaccination strategies on the basis of local data and priority populations for protection. This is the objective of the PERILIC (PERtussis Immunization programs in Low income Countries) project, a study led by Dr. Fabien Taieb from the Institut Pasteur Translational Research Center.

Since its 2016 launch in Cambodia, Togo, Iran and Madagascar, almost 600 infants have been diagnosed using molecular biology. The same goes for 450 contacts of these infants in the case of positive samples for *Bordetella pertussis* or B. parapertussis. Samples have been taken from almost 4,000 children and adolescents as part of a sero-epidemiological investigation.

The initial results, which are currently being analyzed, reveal a circulation of the disease in these countries, which is difficult to demonstrate due to the lack of a specific clinical presentation. These data will make clinicians and health authorities more aware of the relevance of this disease in low income countries, where its epidemiological surveillance is rare or even inexistent. In December 2018, Ivory Coast joined the program.

Leptospirosis:
a worrying neglected disease

Infecting one person every 30 seconds and responsible for one death every 9 minutes, leptospirosis is a worrying bacterial infection that emerges in the tropics. Its mortality rate, higher than that of other tropical infections, can reach 5 to 15%, versus 0.2% for malaria, less than 0.1% for dengue and less than 5% for Chagas disease. Despite the heavy burden it represents, leptospirosis remains a seriously neglected disease, as the research resources dedicated to it are 24 times[1] less than what is needed. The Network's institutes have pooled their efforts to raise awareness of this disease.

A zoonosis of bacterial origin provoked by several pathogenic species of *Leptospira,* leptospirosis is mainly present in the tropics and in developing countries where poor sanitary conditions and substandard housing can be found. *Leptospira* pathogens are excreted in the urine of infected animals, thus contaminating the environment. Almost all mammals are potential reservoirs of the disease. Humans can contract it through exposure to water or mud contaminated by the urine of an infected animal. The incidence of leptospirosis is expected to rise due to the increase in extreme weather events, causing floods, and rapid, poor quality urbanization, which have created the ideal conditions for its transmission by rodents in slums.

The clinical manifestations of leptospirosis are not specific. They range from influenza symptoms to kidney failure, like many other infectious diseases including dengue and malaria. It is generally diagnosed through the detection of antibodies in serum or bacterial DNA using PCR[2]. Antibiotic treatment exists, and a simple administration of penicillin, tetracycline or azithromycin in the early stages of the disease treats it effectively. Human vaccines are also available, but present weak serological specificity and do not provide long-term cross immunity.

Land use and the climate are critical factors for the emergence of the disease. Against this background, the Institut Pasteur in Paris coordinates the regional ECOMORE 2 project, funded by the French Development Agency (AFD). Teams from the National Institute of Hygiene Epidemiology (NIHE) in Hanoi, Vietnam, and the Burmese National Health Laboratory (NHL) are currently carrying out a comparative study on the risk of contamination in urban areas and rural areas undergoing urbanization - areas that are particularly affected by heavy rain and flooding.

At the Institut Pasteur de Nouvelle Calédonie (IPNC), a region where leptospirosis is hyperendemic, research is focused on the role of the environment as a major factor in human contamination. Rather than studying leptospirosis as a zoonosis, it should in fact be considered as a bacterial infection tied to the ecosystem. The capacity of various terrestrial and aquatic ecosystems to support the survival of *Leptospira* is currently being studied at the IPNC and has enabled researchers to isolate 18 new species of the genus[3][5]. This work helps to determine the terrestrial/aquatic habitat preferred by virulent leptospirosis to develop risk management strategies.

RAISING AWARENESS OF THE LEPTOSPIROSIS CRISIS: AN URGENT ISSUE

Although leptospirosis cannot be eradicated as it is impossible to eliminate rats, which are its reservoir, its burden can be considerably alleviated through better access to diagnostics and public interventions, such as social and health actions and the allocation of specific funds.
In 2018, as part of the efforts to raise awareness of this neglected disease, leptospirosis was identified by the Network's Board of Directors as a model for a mobilization of the Network on a global scale according to a *one health* ecosystem approach. The main objective of this is to tackle the specificities of this disease and its determining factors to the extent that they appear in the various ecosystems in which the Network is located. A full program to meet this objective is being established.

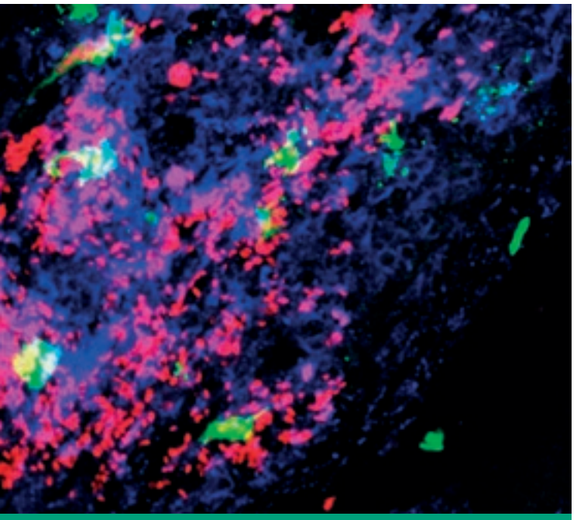
The Institut Pasteur de Montevideo, Uruguay, studies leptospirosis using three complementary approaches: fundamental research, veterinary microbiology and microbial genomics. Understanding how leptospires move in the water and how they experience their environment and react to it (in particular in terms of regulating virulence) guides fundamental research efforts in the hunt for the mechanisms responsible for the disease. As Uruguay is one of the top 10 beef exporters in the world, leptospirosis in its herds (c.20 % of cattle are infected) has significant economic repercussions. Over 65 pathogenic strains were recently isolated in the beef and milk cow population, highlighting how urgent it is to reformulate the veterinary vaccines that indirectly provide protection from human leptospirosis[4]. Whole genome sequencing for all these strains will improve diagnostics through the association of genetics with variations in serological response.

The Institut Pasteur in Paris has many years of experience in leptospirosis research: the microscopic agglutination test (MAT) – the reference test for serological diagnosis of the disease – was developed by Martin and Pettit in 1917. The only human vaccine on the market was produced in the 1980s. Today, the Spirochete biology unit, which has described several virulence factors, is a recognized leader in the field of *Leptospira* genetics. This unit also covers the National Reference Center for Leptospirosis. By comparing the genomes of *Leptospira* isolated from different environmental sources across the world, the team was recently able to identify several new species of *Leptospira* with the assistance of a new junior group from the INRS Armand Frappier Health and Biotechnology Center in Canada[5]. Pooling their knowledge and data through the Network, they are continuing their joint efforts to understand the evolution of this subgroup of the species into pathogens and their adaptation to different hosts.

1 Leptospirosis under the bibliometrics radar: evidence for a vicious circle of neglect. *Goarant C. & al.* Journal of Global Health, *juin 2019. Doi : 10.7189/jogh.09.010302*
2 Réaction en chaîne par polyménase.
3 Deciphering the unexplored Leptospira diversity from soils uncovers genomic evolution to virulence. *Thibeaux R., Iraola G. et al.* Microbial Genomics, *3 janvier 2018. Doi : 10.1099/mgen.0.000144.*
4 Isolation of pathogenic Leptospira strains from naturally infected cattle in Uruguay reveals high serovar diversity, and uncovers a relevant risk for human leptospirosis. *Zarantonelli L., Suanes A., Meny P., Buroni F. et al.* PLoS Neglected Tropical Diseases, *13 septembre 2018. Doi : 10.1371/journal.pntd.0006694.*
5 Revisiting the taxonomy and evolution of pathogenicity of the genus Leptospira through the prism of genomics. *Vincent A.T, Schiettekatte O. et al.* PLoS Neglected Tropical Diseases, *23 mai 2019. Doi : 10.1371/journal.pntd.0007270.*

Fighting leishmaniasis, **a global scourge**

Leishmaniasis is a zoonotic parasitic disease caused by *Leishmania* parasites, of which there are several species. These parasites are unicellular organisms and, as eukaryotes, are classed in the same domain as animals and humans.
Treating leishmaniasis is therefore particularly difficult as the treatments to which Leishmania are increasingly resistant are also very toxic to humans.

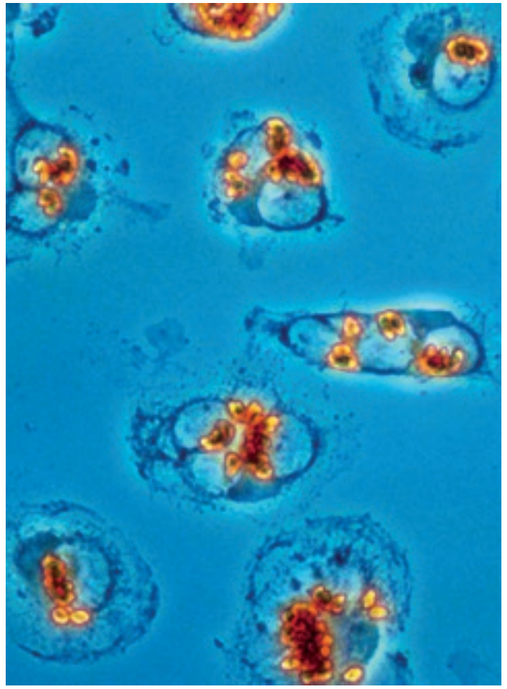


A NEGLECTED DISEASE THAT HITS THE POOREST

WHO estimates the number of people with leishmaniasis in the world at 12 million, and 2 million new cases are recorded annually. It causes 50,000 to 70,000 deaths each year. But these figures are probably underestimated: there are major endemic areas where the disease is particularly present and these areas generally correspond to a “poverty map”: South America, North Africa, East Africa, India. Mortality attributable to leishmaniasis is particularly high in the latter two territories. Leishmaniasis thus concerns populations with little access to medical diagnostics and appropriate treatments above all. But today, environmental changes like urbanization and climate change are modifying the epidemiology of the disease, and highlight the need to support research to effectively fight leishmaniasis.

These parasites, which can live for a long time in their hosts, often asymptomatically, are responsible for chronic diseases that can be highly debilitating or even fatal. This is why their cost to the economy, still poorly understood *(see box)*, is thought to be significant.

Transmitted by insects, Phlebotominae, the parasites can be responsible for three types of leishmaniasis: cutaneous (with ulcers and disfiguring lesions that can become infected), mucocutaneous (principally affecting the nose) and visceral. The latter is fatal if not correctly treated. It is often mistaken for malaria, as it causes fever, weight loss associated with lack of appetite, and inflammation of the liver and spleen.



Gérald Spaeth

Director of the Molecular Parasitology and Signaling Unit, Institut Pasteur

How does leishmaniasis adapt to its environment?

In North Africa, where there are thousands of new cases each year, it is a true public health issue, while France still only records around one hundred patients per year.
The disease is now considered an emerging disease in Europe, notably due to the change of various environmental and climate factors.
The parasites are not very pathogenic to humans and mainly infect dogs. However, the surge in human cases in some regions is also tied to the extraordinary genomic plasticity of these parasites, which enables them to adapt rapidly to environmental changes and frequently develop resistance to antiparasite treatments. Better understanding the mechanisms of adaptation of Leishmania is at the heart of the LeiSHield project, developed by the Institut Pasteur.

How is the fight against leishmaniasis organized within the Institut Pasteur International Network?

We started by collaborating with researchers working on the subject within the Network, with the objective of studying the phenotype variability of Leishmania. This collaboration gave rise to a website (LeishRIIP (www.leishriip.org), enabling us to pool current knowledge on the disease. A group of researchers then took on the task of developing the LeiSHield project, with a view to explaining the genetic changes observed in Leishmania isolates collected in various Network institutes. We showed that these parasites had a unique genomic instability mechanism.
Work carried out during the project’s pilot phase, with 16 partners including the Institut Pasteur in Paris, in Morocco, in Algeria, in Tunisia and in Greece and the Oswaldo Cruz Foundation (FioCruz) in Brazil, could be highlighted and shared in a recent publication[1].

How does the Horizon 2020 program support research?

In 2017, we received €1.7 million over 4 years in funding from the European Union, as part of the Horizon 2020 research and innovation project.
The LeiSHield pilot project thus became H2020 LeiSHield-MATI (Morocco, Algeria, Tunisia, Iran), which started in April 2018 (www.leishield.org). It was designed to implement staff mobility and technology transfers and establish collaborations between researchers.
Its scope of research is more geographically limited than before, but three new research topics have been added: transmission of the parasite by insects, potential reservoir animals in endemic zones and immune response in humans.

1 Leishmania Genome Dynamics during Environmental Adaptation Reveal Strain-Specific Differences in Genes Copy Number Variation, Karyotype Instability and Telomeric Amplification. G Bussoti & al. mBio, *2018. DOI: 10.1128/mBio. 01399-1.*

Chronic malnutrition in children: **a new microbial signature in the gut**

Chronic malnutrition, often associated with inflammation of the small intestine, affects one child under five years of age in four. The leading cause of child mortality in low income countries, it is also responsible for significant developmental anomalies. To better understand the underlying mechanisms of chronic malnutrition and improve its management, the Afribiota project was established in 2016, led by the Institut Pasteur in Paris, Madagascar and Bangui. Its first results were published in 2018 in PNAS.

The study reveals the disturbances experienced by the microbiota of malnourished children, as well as the existence of a surprising microbial signature in the gut, characterized by the massive presence of bacteria ordinarily associated with the nose and mouth.

Chronic malnutrition is responsible for over 3 million deaths every year around the world and causes cognitive and physical developmental anomalies such as stunted growth, which are difficult to overcome. Chronic malnutrition is not only tied to food problems, but also immune issues and chronic intestinal inflammation. Researchers have looked at the intestinal flora of children in order to characterize the bacterial populations that colonize the small intestine of malnourished children.

In these children, there is intestinal inflammation. The villi of the small intestine in particular atrophy, so it can no longer fulfil its role in the digestion and absorption of nutrients. *"We were unaware of the extent to which the usual bacterial populations were modified"* indicates Philippe Sansonetti, medical doctor and microbiological researcher at the Institut Pasteur Molecular Microbial Pathogenesis he leads, and professor at the Collège de France in Paris.
The microbiote of 980 children living in Tananarive (Madagascar) and Bangui (Central African Republic), both with and without issues of chronic malnutrition, were analyzed. Bacterial cultures and metagenomic analyses, which reveal all of the microbial species present, have delivered surprising results: *"In malnourished children, we expected to see an increase in enteropathogenic bacteria, such as Campylobacter, Shigella and Salmonella,"* comments Pascale Vonaesch, doctor of microbiology in the Institut Pasteur Molecular Microbial Pathogenesis unit. *"But certainly not oropharyngeal bacteria!"*. This type of phenomenon has already been observed in some inflammatory intestinal diseases and colon cancer, but never on such a massive scale. *"The bacteria are present at 10 to 100 times the amount found in controls"*, states Philippe Sansonetti.

AFRIBIOTA
is supported by the Total Foundation, Odyssey Reinsurance Company, the Institut Pasteur, the Nutricia Research Foundation, the Petram Foundation and the Bill & Melinda Gates Foundation.

Oropharyngeal bacteria have therefore crossed the barriers that usually confine them to the nose, pharynx and mouth, migrating to and colonizing the stomach and intestine. This massive, unusual migration is observed in malnourished children regardless of their origin, Malagasy or Central African, their dietary habits and their environment.
We know that children affected by malnutrition often also have poor oral hygiene and recurring rhinopharyngitis. Initial hypotheses can be drawn: *"There may be an excess growth of oral and rhinopharyngeal flora, which is then swallowed and, as there is no effective control, travels to the digestive system"*, suggests Philippe Sansonetti. This information is useful for then being able to deliver effective preventive messages.

Ultimately, this bacterial signature in the gut, in addition to data from epidemiological, immunological, anthropological, and psychomotor development studies, should help to better understand the causes of chronic malnutrition, facilitate its diagnosis and finally better treat this global scourge.

Better management of primary immunodeficiencies in Tunisia

Primary immunodeficiencies are disorders that lead to anomalies affecting the development and/or maturation of immune system cells. There are over 300 different genetic diseases under this definition, which are common in Tunisia due to the high rate of consanguinity. They mainly affect young children who experience severe, sometimes fatal, recurring infections. In the face of these diseases, a team from the Institut Pasteur de Tunis led by Prof. Ridha Barbouche is carrying out research to improve their diagnosis, treatment and prevention. The ATun-DIPs (Improving the Care of Tunisian Children with Primary Immunodeficiencies) project, funded by the Principality of Monaco, aims to reinforce diagnosis and care capacities for children with primary immunodeficiencies in central and south Tunisia.

The project has shown that there has been a clear progression in the number of patients suspected of having a primary immunodeficiency: 521 in 2017 (up 19% on 2016). The number of new cases with a diagnosis confirmed by immunological testing has progressed from 60 cases in 2016 to 67 in 2017. The informing of various stakeholders about primary immunodeficiencies as part of the project has contributed to better awareness of the diseases through training targeted at doctors, nurses and patients' families.

Finally, the creation, as part of the project, of a patient association is a major asset for the sustainability of the action. A second phase is planned in order to improve molecular diagnostics – which will help to confirm a significant number of unlabeled cases – and widen the scope of the project to include the north and west of the country, in partnership with the Tunis Faculty of Medicine.

Develop

The Network's institutes contribute to the reinforcing of scientific capacities, in particular through training. In a competitive international context, the Network is also committed to developing technological resources and implementing collaborative programs to support the scientists of tomorrow.

"In 2017, the Institut Pasteur de Madagascar was on the front lines of the fight against the plague epidemic that hit the island. And there are many other examples that demonstrate the mobilization of the International Network alongside local and international partners and, of course, with the support of the Institut Pasteur in Paris. Beyond emergency situations, Network institutes aim to address the health concerns of the local population, wherever they are located, in a sustainable way. They do so through research, but also by the training of local young scientists. This training through research is one of the fundamental missions of the Institut Pasteur and the Network, and an essential element to the strengthening of health systems."

PROF. FRANÇOISE BARRÉ-SINOUSSI,
Honorary President of the Institut Pasteur International Network
Institut Pasteur 130 year anniversary ceremony, November 14, 2018

Training human resources and supporting **scientific careers**

The Network has participated in training and supported scientists in their careers for many years through courses and mobility programs. True to the Pasteurian mission of education, the Network institutes contribute to enhancing scientific capacities and human resources across the world in order to find sustainable approaches for local populations.

TRAINING: A PRIORITY FOR THE NETWORK

Training programs are provided in the institutes in partnership with national universities and local players in scientific research. They are open to researchers, technicians and students from other institutions. Many Network institutes are host laboratories for university students at the bachelor, master and doctoral level. Network institute researchers also participate in training specialists with postgraduate level courses and seminars. There are several centers dedicated to training and welcoming interns in the Network (Cameroon, Madagascar, Niger, Ivory Coast, Bangui, Cambodia, Korea, Vietnam, Montevideo, etc.).

ENCOURAGING MOBILITY

Each year, the Department of International Affairs of the Institut Pasteur offers funding (Calmette & Yersin program) and mobility aids to promote and facilitate the completion of theses, post-doctorates, internships and training within a Network institute, for scientists (students, researchers, engineers and technicians).

To strengthen its relationship with the Network, in 2014 the Institut Pasteur initiated a program aiming to offer each newly recruited researcher the opportunity to carry out a 3-month scientific mission in a Network institute. In 2017 and 2018, eight new recruits carried out three-month missions within the Network.

The **Calmette & Yersin doctoral and postdoctoral program** funds short-term (for internships and study) and long-term (doctoral and postdoctoral) mobility for scientists and students who wish to train and work at a Network institute. Its main objective is to promote the mobility of Network scientists within the Network.

A product of the partnership between the Foundation of France and Institut Pasteur, the **Pierre Ledoux Jeunesse Internationale Foundation scholarships** attributed fund biomedical research internships for French students in a country with limited resources within the Network.

The **Pasteur International Network** association finances between 10 and 20 courses per year, organized by member institutes. For example, an international medical entomology course has taken place within the Network at the Institut Pasteur du Laos since 2018, alternating with the course at the Institut Pasteur in Paris. In the same year, the Institut Pasteur medical entomology course celebrated its 30th year. Since 1988, this course, in different forms, has welcomed 173 students, 38% of whom came from within the Institut Pasteur International Network and almost one third from Africa.

OMICS DATA: TRAINING AND RAISING AWARENESS WITH THE H2020 PHINDACCESS PROJECT[1]

In order to develop optimized surveillance tools for better controlling infectious diseases such as leishmaniasis, tuberculosis etc., the Institut Pasteur in Tunis is coordinating the PHINDaccess project. Various activities will be carried out from 2018 to 2021, in close collaboration with the Institut Pasteur, the Center for Genomic Regulation (CRG), the Max Planck Institute for Molecular Genetics (MPG) and the Robert Koch Institute (RKI). The aim of this project is to position the IPT as a center of excellence in the field of Omics data analysis and exploitation applied to the study of infectious diseases and host-pathogen interactions, through the organization of training, internships, expert missions and scientific dissemination activities.

1 www.phindaccess.org

A LONG-TERM COMMITMENT

The Institut Pasteur Department of International Affairs is committed to the development of professional career paths for scientists in the Network, with the implementation of programs designed to attract talented young scientists and reveal scientific leaders *(see pages 54-56)*. At the same time, an international Pasteurian course label is under consideration with the aim of highlighting the specificity and quality of Pasteurian teaching in the eyes of the international community.

116
scientists and students benefited from an international grant in 2017-2018

95
recipients of the Calmette & Yersin program:

- **42** scholarships for taking courses
- **53** internship funds **17** of which are doctoral grants for 3 years and **2** postdoctoral grants for 2 years

21
grants co-financed by the Institut Pasteur Department of International Affairs and partners:

- **17** scholarships from the Pierre Ledoux Jeunesse Internationale Foundation
- **4** grants for the International Cooperation of the Principality of Monaco

8
3-month missions for new recruits

4-year research groups (G4) for developing **innovative projects**

As a unique model of cooperation in healthcare, the Institut Pasteur International Network brings together a human and scientific community working on both local and international priorities in the field of health. In order to support the talents of tomorrow in the Network, a specific funding program was implemented in 2013: 4-year research groups. Since its launch, seven G4s have been created.

A SPRINGBOARD FOR RESEARCHERS

The 4-year research group (G4) funding program offers talented young scientists a place in the Institut Pasteur International Network. Researchers develop their ambitious projects with a competitive team they put together themselves. The G4 is a major asset for launching a career within the Network.

DYNAMIC INTERNATIONAL RESEARCH

The creation of a G4 contributes to the emergence of new expertise and/or the reinforcement of skills through training for local teams at host institutes. It promotes transdisciplinary research and regional, national and international scientific partnerships. 4-year groups also contribute to the increased international visibility of the institutes concerned.

The **selection** of a G4 is carried out by a selection committee that evaluates the applications received following a **call for applications** open to young researchers with international postdoctoral experience who wish to develop their career within the Network. This is defined jointly with partners and offers an opportunity for cofinancing by a third-party organization. A steering committee supports the winner and monitors the progress of the G4.

RESEARCH GROUPS

Lawrence Ayong / **G4 2013-2017**
Pasteur Center in Cameroon / Malaria research group

Ousmane Ndiath / **G4 2013-2017**
Institut Pasteur de Madagascar / Malaria vector control

Tineke Cantaert / **G4 2015-2019**
Institut Pasteur du Cambodge / Immunology research group

Cheikh Loucoubar / **G4 2015-2019**
Institut Pasteur de Dakar / Biostatistics, bioinformatics and modeling

Gary Wong / **G4 2018-2022**
Institut Pasteur of Shanghai / Chinese Academy of Sciences / Strengthened cooperation in the field of emerging and infectious diseases

Jean-Pierre Peron / **G4 2019-2023**
Pasteur-University of São Paulo scientific platform/ Arbovirus neuroimmunology

Amy Bei / **G4 2019-2023**
Institut Pasteur de Dakar / Evaluating access to candidate vaccine in West Africa

"The G4 is an excellent initiative for supporting young scientists. It provides the right environment for launching innovative research projects with high added value for the host institute."

Gary Wong, Institut Pasteur of Shanghai, Chinese Academy of Sciences, G4 2018

Tineke Cantaert

4-year research group (G4) – Immunology
Institut Pasteur du Cambodge

What G4 have you implemented?

In early 2015, I created my own 4-year research group (G4) at the Institut Pasteur du Cambodge. The objective was to strengthen fundamental immunology research within the Network, focusing on infectious diseases in low to middle income countries. Dengue is an arboviral disease with significant socioeconomic impact in countries like Cambodia.
It is not symptomatic in all infected individuals and is probably attributable to an abnormal immune response.
The research of my G4 has looked at the definition of a protective immune response schema and the mechanisms leading to pathology after infection.
There are many challenges to be overcome in this context, such as identifying the biomarkers of a protective immune response and implementing new tools for monitoring cases in order to better understand the disease with a view to developing new vaccines.

What results have you obtained and what are the next steps?

In collaboration with researchers from the Institut Pasteur du Cambodge and the Institut Pasteur in Paris, we have identified the specific immune signatures associated with a protective immune response after infection. The differences observed in terms of adaptive immune response in asymptomatic individuals is thought to contribute to containing the virus and avoiding the development of the immunopathology. By re-examining the behavior of the virus, we have been able to show that the infection alters the functions of B cells independently of antibodies.
With researchers from the University of Groningen in the Netherlands, we have identified a new virus receptor and described its role in the disease process. Today, we are studying new biomarkers to evaluate the severity of the disease, which can be used for patient management, in association with the Network. On the basis of these results, we are working with the Rockefeller University (United States) and the Institut Pasteur in Paris to refine the immune signatures. In parallel, we plan to test a new candidate vaccine against dengue in non-human primates with researchers from St. Luke's Medical Center in the Philippines and the Institut Pasteur in Paris.

How does the G4 represent a career springboard and a local asset?

The G4 has offered me the opportunity to carry out my own research at the Institut Pasteur du Cambodge. Its success is thanks to strong local support from management and research groups there, including the Virology unit and the Epidemiology and Public Health unit. They supported me in making the connection between field research and laboratory research. Thanks to the results obtained and collaborations initiated, I secured the position of Howard Hughes Medical Institute/Wellcome International Research Scholar in 2017 and won the International Union of Immunological Societies Early Career Research Prize in Vaccinology in 2018. These grants will assure the continuation of the research now that the G4 has ended.
In October 2018, the G4 merged with the Institut Pasteur du Cambodge immunology platform to form a new unit. Research into host immune responses to infectious diseases at the Institut Pasteur du Cambodge is therefore reinforced. Furthermore, we are committed to continuing the training of the Cambodian and regional Master and PhD students in our team.

International Joint Research Units
for strengthening partnerships

International Joint Research Units were created in 2016 with the aim of constructing or reinforcing international scientific partnerships. They pair a team from the Institute Pasteur with a team from an international or Network institution. To strengthen this scheme and develop actions that implement the Network's scientific strategy and/or meet priority regional public health needs, the Institut Pasteur will support the creating of new Pasteur International Joint Research Units (PIU).

PROMOTING PARTNERSHIPS FOR EXCELLENCE AT AN INTERNATIONAL LEVEL

A PIU is a "virtual unit" designed to pair a Pasteur unit with at least one international research team with complementary competencies and expertise to elaborate research programs on shared topics of interest and mobilize national and international funding to implement their shared research projects.
Built around scientific projects selected for their quality, these research units facilitate scientific interactions and mobility, particularly for young researchers, and give greater visibility to the research teams involved.
A PIU provides a five-year partnership framework and facilitates the mobility of scientists between partner institutes as well as communications with local universities and research institutes.

THE SIX STRUCTURES CREATED

2016

Malaria Translational Research Unit (MTRU):
Evolution and adaptation of Plasmodium parasites to their host.
Jean-Christophe BARALE, Institut Pasteur (Paris) and Didier MENARD / Benoît WITKOWSKI, Institut Pasteur du Cambodge.

Integrative Microbiology of Zoonotic Pathogens Unit (IMiZA):
Leptospirosis and the persistence of leptospires in the environment.
Mathieu PICARDEAU, Institut Pasteur (Paris), and Alejandro BUSCHIAZZO, Institut Pasteur de Montevideo.

Inflammation and Leishmania infection Unit (InflaLeish):
Study of interactions between Leismania parasites and their host.
Gérald SPAETH, Institut Pasteur (Paris) and Guangxun MENG, Institut Pasteur of Shanghai – Chinese Academy of Sciences.

Vaccinomics Unit:
Understanding the immunological mechanisms involved in the heterogeneity of vaccine response.
Anavaj SAKUNTABHAI, Institut Pasteur (Paris) and Fumihiko MATSUDA, Kyoto University, Japan.

2017

Artificial Virus EvolutioN Unit (AVENUe):
Study of the natural evolution of viruses with synthetic biology.
Marco VIGNUZZI, Institut Pasteur (Paris) and Benjamin TENOEVER, Icahn School of Medecine at Mount Sinai, USA.

2018

Mucosal Immunomics Laboratory (MIL):
Genetic, environmental and local microbiome factors involved in respiratory immune response.
Lars ROGGE, Institut Pasteur (Paris) and Hiroshi KIYONO, Institute of Medical Sciences at the University of Tokyo (IMSUT), Japan

Scientific platforms
for sharing resources

Institut Pasteur International Network institutes have scientific platforms for carrying out cutting edge research and sharing their resources. They are increasingly called upon to pool their infrastructures to share their expertise across the Network.

A vectopole dedicated
to vector ecology in French Guiana

Inaugurated in 2014, this 500 m^2 building enables the Institut Pasteur to continue a tradition of medical entomology dating back to the 1940s in French Guiana. In line with this history, the Émile Abonnenc Amazonian Vectopole is continuing with molecular taxonomy work to decode roughly 80 local species of mosquito is the Culex genus. Another of its missions is to monitor the resistance of vector mosquitoes and understand its mechanisms. More recently, it has focused on vectorial competence for the transmission of arboviruses, for example chikungunya, Zika, dengue and yellow fever, as well as the associated behavioral modifications. To accomplish these tasks, the vectopole has, in addition to biological laboratories, a dedicated insecticides area, a priceless and unique collection of mosquito specimens, and a biosafety level 3 insectarium for experimenting with insect infections and testing *Wolbachia* bacteria on local species and strains *(see page 35)*. Since 2017, it has also been home to a 5-year group (G5) studying bacteria specific to mosquitoes[1].

1 https://www.pasteur-cayenne.fr/la-recherche/nos-equipes/uem/vectopole/

Screening platforms for the discovery
of new drugs in Korea and Lille

The Institut Pasteur Korea[1] is recognized for its expertise in the use of imaging technology for chemico-genomic phenotype screening. This involves the simultaneous reaction of a large number of molecules (> 500,000) with cell cultures, and observation of the result. These technologies are used in fundamental research and for the discovery of new drugs for treatment purposes. The Institut Pasteur Korea is currently focusing on diseases such as tuberculosis, hepatitis, influenza, cancer, dengue and orphan diseases, as well as emerging diseases.

A similar platform has been set up at the Institut Pasteur de Lille[2]. Its mission is to develop and study compounds and designed to target new molecules for the treatment of infectious and metabolic diseases. For this, the institute has a "chemical library" of over 90,000 compounds and different screening units.

1 http://www.ip-korea.org/RDP/lab_screening.php
2 https://www.pasteur-lille.fr/recherche-medicale/plateforme-technologique/

Biological research meets big data in Paris

IT tools are now so powerful, and the amount of data so vast, that modeling and statistical analysis could sometimes even be used in place of laboratory experiments. Or be even more effective... The Institut Pasteur therefore made a commitment to working with big data in 2015, with the creation of the Bioinformatics, biostatistics and integrative biology center (C3BI), which became the Department of Computational Biology[1]. This scientific platform works as both a service provider, for the on-request analysis and modeling of biological data collected on the ground by Institut Pasteur International Network teams, and as a research center in its own right. The department thus coordinates the INCEPTION (INstitut Convergence: Emergence of Pathology Through Individuals and Populations) project. With this project, the vast mass of data originating from experimental biology, public health and clinical research is used to understand and monitor the appearance of diseases in populations and individuals. Since 2018, teams have worked in one of the two buildings on the Paris campus forming the “Omics” unit; the second is occupied by the Biomics division, dedicated to sequencing. The latter works in five fields: genomics (DNA sequencing of microorganisms, bacteria, fungi, parasites and viruses), transcriptomics (RNA analysis), epigenomics (analysis of epigenetic changes to DNA), genotyping (analysis of genetic polymorphisms in humans and mice) and metagenomics (characterization of communities of microorganisms).

1 https://www.pasteur.fr/fr/nos-missions/recherche/departement-biologie-computationnelle

Unique biological collections

The Network is home to numerous biological resources. For example, in Brussels, Sciensano has one of the largest collections of medically interesting BCCM/IHEM in the world. A public collection created in 1980, this brings together almost 16,000 references, representing over 1,500 different species. It includes pathogenic yeasts and molds, mycotoxin producing species, allergenic strains and contaminants from the human environment[1]. Efforts to highlight the value of biological collections have given rise to the PIBnet pilot project[2] (see testimonial), covering eight Network institutes[3].

1 http://bccm.belspo.be/about-us/bccm-ihem
2 Pasteur International Bioresources network: http://www.msdavenir.fr/programme-de-recherche/projet-pibnet/
3 Ivory Coast, Guinea, Madagascar, Tunisia, Senegal, Cameroon, Cambodia, France - French Guiana.

Spencer Shorte

Scientific Director of the Institut Pasteur Korea

Why do members of the Network have scientific platforms?

Very simply because sharing resources between Institut Pasteur institutions and other partners means we can reduce costs and optimize the use of equipment, as well as the necessary expertise.
If each Institut Pasteur had to buy all the equipment it needs to carry out its research, not only would that be very expensive, but the equipment would undoubtedly be underused.

It’s quite an innovative approach...

Yes, the sharing of resources between different players is a relatively recent approach in the scientific world, but the Institut Pasteur was a real trailblazer in this area: its first scientific platform was created back in 1929 in Marne-la-Coquette (France). That was a biological micro-cinematography laboratory.

What challenges do Network scientific platforms have to overcome?

We will be called upon to share more and more in the future: procedures, field samples, expertise, analysis results... This will probably require great organization and coordination efforts. These efforts have started to be put in place, for example with PIBnet[2], a platform that identifies all the Network’s biological collections (microorganisms and human, animal, plant and environmental samples) and the analysis data associated with them.
But we still need to establish a cost-sharing model that would be more encouraging. Today, our greatest challenge lies in creating tools that would enable us to trace the origin, conservation, history and usefulness of shared scientific resources.
The systematic sharing of scientific resources will revolutionize research methods. It will lead to better recognition of the work of the teams that participate at every stage of the long research process to the publication of data. Between this and progress in the field of IT, we will thus improve the quality of scientific production, with health benefits for local populations, while ensuring the reproducibility and accuracy of results.

Partnerships - **an essential component**

The implementation of ambitious, sustainable partnerships is an essential prerequisite for developing the Network for the benefit of local populations. Some examples are given below.

MINISTRIES AND GOVERNMENT AGENCIES IN FRANCE AND ABROAD

Chinese Academy of Sciences (CAS) • African Academy of Sciences (AAS) • French Development Agency (AFD) • French Research Agency (ANR) • French Agency for AIDS and Viral Hepatitis Research (ANRS) • Japanese International Cooperation Agency (JICA) • Africa Centers for Disease Control and Prevention (Africa CDC) • American Center for Disease Control (CDC) • Assistant Secretary for Preparedness and Response within the Department of Health and Human Services (ASPR/DHHS) • Expertise France • French Ministry of Europe and Foreign Affairs • French Ministry of Higher Education, Research and Innovation • US Agency for International Development (Usaid) • Monaco Department of International Cooperation • Ministries of Health and Research in the countries in which Network institutes are located

RESEARCH INSTITUTIONS

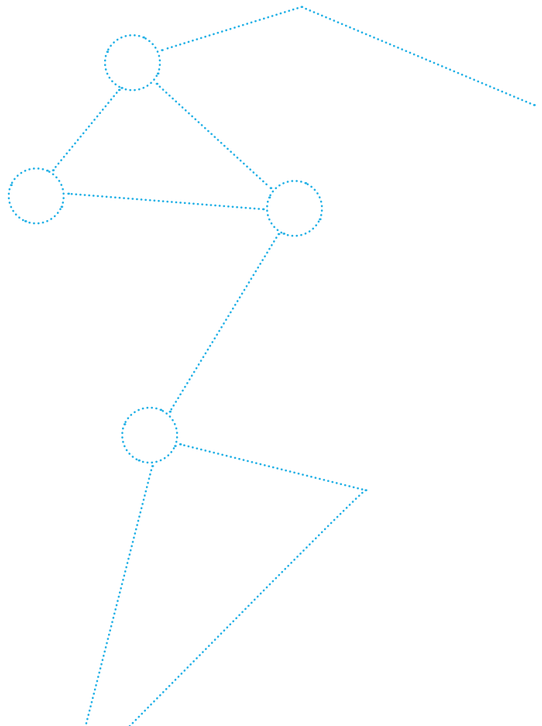
All member institutions of AVIESAN • French Center for Space Studies (CNES) • University of Sao Paulo (Brazil) • University of Tokyo and University of Kyoto (Japan) • Japanese Research Institution for Science and Technology (Riken) • National Center for Global Health and Medicine (Japan) • The Peter Doherty institute for infection and immunity (Australia) • Monash university (Australia) • Griffith university (Australia) • Walter & Eliza Hall institute of medical research (Australia) • University of Hong Kong

INTERNATIONAL ORGANIZATIONS

World Health Organization (WHO) • World Organization for Animal Health (OIE) • European Commission • The Global Fund • National Institutes of Health (NIH) • European & Developing Countries Clinical Trials Partnership (EDCTP) • Global Alliance for Vaccines & Immunization (GAVI) • Food and Agriculture Organization of the United Nations (FAO)

FOUNDATIONS, ASSOCIATIONS AND NGOS

Francophone University Association (AUF) • Agency of Preventive Medicine (AMP) • Bill & Melinda Gates Foundation • Scientific Center of Monaco (CSM) • Drugs for Neglected Diseases initiative (DNDi) • Fondation de France • Mérieux Foundation • Michelin Corporate Foundation • Pierre Ledoux Jeunesse internationale Foundation • Petram Foundation • Prince Albert II of Monaco Foundation • Rotary International Foundation and District 1660 Rotary Clubs • Sanofi Espoir Foundation • Total Foundation • MSDAvenir • Nutricia Research Foundation • São Paulo Research Foundation (FAPESP) • Wellcome Trust



Network Directors and SCIENTIFIC DIRECTORS

AFRICA

- **Institut Pasteur de Bangui,** Jean-Pierre LOMBART (Director) • Emmanuel NAKOUNÉ (Scientific Director)
- **Pasteur Center in Cameroon,** Élisabeth CARNIEL • Sara EYANGOH
- **CERMES Niger,** Halima BOUBACAR followed by Rabiou LABBO (Interim) • Jean TESTA
- **Institut Pasteur de Côte d'Ivoire,** Mireille DOSSO
- **Institut Pasteur de Dakar,** Amadou SALL • Christophe PEYREFITTE
- **Institut Pasteur de Guinée,** Noël TORDO
- **Institut Pasteur de Madagascar,** André SPIEGEL • Voahangy RASOLOFO

AMERICAS

- **Armand-Frappier Santé Biotechnologie Research Center,** Pierre TALBOT followed by Claude GUERTIN
- **Oswaldo Cruz Foundation (Fiocruz),** Nísia Trindade LIMA (President) • Rodrigo CORREA OLIVEIRA
- **Institut Pasteur de la Guadeloupe,** Antoine TALARMIN
- **Institut Pasteur de la Guyane,** Mirdad KAZANJI
- **Institut Pasteur de Montevideo,** Carlos BATTHYANY

ASIA

- **Hong Kong University-Pasteur Research Center,** Malik PEIRIS and Roberto BRUZZONE (co-directors)
- **Institut Pasteur du Cambodge,** Didier FONTENILLE followed by Laurence BARIL
- **Institut Pasteur Korea,** Wang-Shick RYU • Spencer SHORTE
- **National Institute of Hygiene and Epidemiology (Hanoi),** Dang Duc ANH
- **Institut Pasteur in Ho Chi Minh City,** Phan Trong LAN • Vu Thi QUE HUONG
- **Institut Pasteur in Nha Trang,** Vien Quang MAI followed by Do Thai HUNG
- **Institut Pasteur de Nouvelle-Calédonie,** Vincent RICHARD followed by Marc JOUAN
- **Institut Pasteur of Shanghai – Chinese Academy of Sciences,** Hong TANG and Fernando ARANZANA-SEISDEDOS (co-directors)
- **Institut Pasteur du Laos,** Paul BREY

EUROPE

- **Institut Pasteur,** Stewart COLE • Olivier SCHWARTZ
- **Institut Pasteur in Italy,** Luigi FRATI • Angela SANTONI
- **Hellenic Institut Pasteur,** Fotini STYLIANOPOULOU • Rebecca MATSAS
- **Institut Pasteur de Lille,** Benoît DEPREZ
- **Institut Pasteur in Saint Petersburg,** Areg TOTOLIAN
- **Stephan Angeloff Institute,** Hristo NAJDENSKI
- **Sciensano,** Myriam SNEYERS

NORTH AFRICA– IRAN

- **Institut Pasteur d'Algérie,** Zoubir HARRAT
- **Institut Pasteur in Iran,** Alireza BIGLARI • Saeid BOUZARI
- **Institut Pasteur du Maroc,** Abderrahmane MAAROUFI
- **Institut Pasteur de Tunis,** Hechmi LOUZIR

logo FSC pending

Institut Pasteur / Department of International Affairs – Institut Pasteur International Network – 25-28, rue du Docteur Roux – 75724 Paris Cedex 15, France. Editor in chief: Juliette Hardy, International Communications Manager, Institut Pasteur. **Photo credits:** Institut Pasteur, AdobeStock/karelnoppe, Alban Orsini, Andreas Müller et Philippe Bousso (p.46 left, Skin infection with *Leishmania major* - red), Arnaud Tarantola, BVA/The Pulses (at Institut Pasteur du Maroc), Christine Schmitt, Anubis Vega Rua, Colourization Jean-Marc Panaud (p. 9 Female mosquito head *Aedes albopictus*, vector of the dengue and chikungunya viruses), CS/The Pulses (at the Hong Kong University-Pasteur Research Pole), Denis Guyenon/The Pulses (at Institut Pasteur de la Guadeloupe), Direction générale de la Santé/Ministère des solidarités et de la santé, Dominique Tardy, François Gardy, Frédéric Veyrier, INRS (p. 44 *Leptospira Interrogans serovar Manilae* cell), Gérald Spaeth, Inmaculada Ortega Pérez, Inova USP/Marcos Santos, Institut Pasteur de Bangui, Institut Pasteur de Bangui/Emmanuel Nakouné Yandoko, Institut Pasteur de Bangui/Jean-Marc Zokoué, Institut Pasteur de Corée, Institut Pasteur de la Guyane, Institut Pasteur de la Nouvelle-Calédonie, Institut Pasteur de Madagascar, Institut Pasteur de Shanghai, Institut Pasteur du Cambodge, Institut Pasteur du Cambodge/Anne Delobel, Institut Pasteur du Cambodge/Jean-Francois Perigois, Institut Pasteur/Marie-Christine Prévost, Ultrastructural Microscopy Platform – Anne Derbise, Yersinia Unit, iStock/AliseFox, Jean-Claude Antoine (p. 46 right, *Leishmania mexicana amazonensis)*, Jean-François Chambon, Kenneth Stapleford and Marco Vignuzzi, Viral Populations and Pathogenesis Unit – Isabelle Bonne et Christine Schmitt, Ultrastructural Microscopy Platform. Colourization Jean-Marc Panaud (p. 13 Chikungunya budding on the surface of mosquito-infected cells *Aedes albopictus)*, Krees Raharison /Institut Pasteur, MediLabSecure, Nabil Zorkot, Pascale Vonaesch, Principauté de Monaco, RHO/The Pulses (at the Institut Pasteur du Laos), SC/The Pulses (at the Institut de Dakar), University of Hong Kong, WHO, William Beaucardet, DR. **Design and production:** VAT - wearetogether.fr - 1906_00035.

This annual report was printed with vegetable ink on Symbol Freelife Satin paper that was produced responsibly.

@institutpasteur
Institut Pasteur
Institut Pasteur
institutpasteur
institutpasteurvideo

Department of International Affairs
Institut Pasteur International Network
25-28, rue du Docteur Roux
75724 Paris Cedex 15, France

www.pasteur.fr