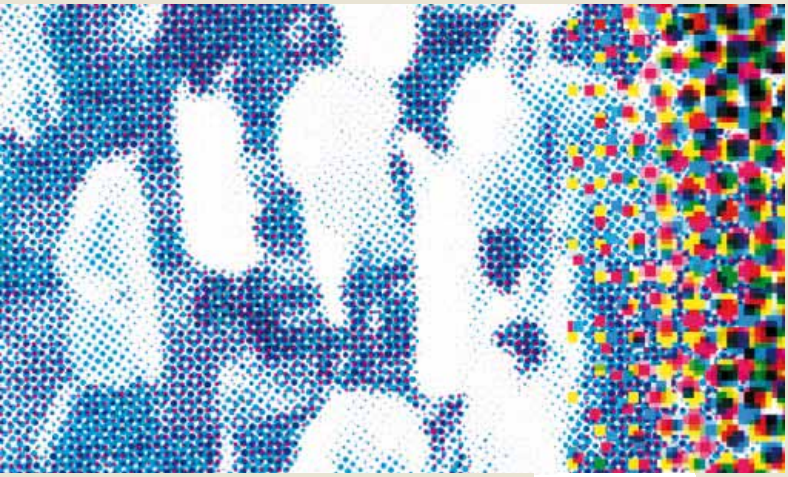

SCIENTIFIC REPORT 2008

international network
Institut Pasteur

SCIENTIFIC REPORT 2008

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LIST OF ABBREVIATIONS

AFD
French Agency for Development

ANRS
French National Agency for Research on AIDS and Viral Hepatitis

BCG
Bacillus Calmette-Guérin (tuberculosis vaccine)

BSL-3
Bio Safety Level 3

CERMES
Medical and Health Research Center (Niamey, Niger)

CIBU
Laboratory for Urgent Response to Biological Threats (Institut Pasteur)

DHHS
U.S. Department of Health and Human Services

EPI
Expanded Program on Immunization (WHO)

FAO
United Nations Food and Agriculture Organization

Fiocruz
Oswaldo Cruz Foundation (Rio de Janeiro, Brazil)

FP-6/7
European Union 6th / 7th Framework Program for Research and Technological Development

HKU-Pasteur Research Center
Hong Kong University-Pasteur Research Center

HTLV-1
Human T cell lymphotropic virus type 1

Institut Pasteur-Shanghai
Institut Pasteur in Shanghai – Chinese Academy of Sciences

INTCR
International Network for Cancer Treatment and Research

NCLE
National Center for Laboratory and Epidemiology (Vientiane, Laos)

NIH
National Institutes of Health (Bethesda, USA)

NIHE
National Institute of Hygiene and Epidemiology (Hanoi, Vietnam)

OIE
World Organization for Animal Health

PCR-(RT)
Polymerase Chain Reaction (Real-Time)

PDVI
Pediatric Dengue Vaccine Initiative

RFLP
Restriction Fragment Length Polymorphism

RIIP
Institut Pasteur International Network

SARS
Severe Acute Respiratory Syndrome

TDR
United Nations Special Program for Research and Training in Tropical Diseases

WHO
World Health Organization

EDITORIAL

ALICE DAUTRY
President of the Institut Pasteur (Paris)

Since its creation in 1888, the Institut Pasteur has been characterized by its openness to the world. Loyal to the idea that science has no homeland, Louis Pasteur hoped that the progress accomplished in the field of health would be shared by all. This view explains the establishment of the first Institut Pasteur abroad, in 1891 in Saigon, followed by many others, all guided by this same spirit.

Today, all member institutes of the Institut Pasteur International Network perform research and surveillance of diseases, prevention and public health activities, and training in the countries and regions where they are located. As such, they are perceived as actors working for international solidarity and inheritors of the spirit of Alexandre Yersin and Charles Nicolle.

But the work of these institutes also benefits the world population as a whole. Since diseases know no borders, it is essential that research and surveillance transcend national boundaries as well. Thus, the Institut Pasteur International Network constitutes a unique tool to promote scientific collaboration. I would like to salute the links of friendship that unite the various institutes and their members, which represent an exceptional wealth for the Network.

Conscious that the fight against disease must be a cooperative effort, we have signed in 2008 a number of conventions with major international partners (Wellcome Trust, Harvard School of Public Health, NIH, CDC, ECDC), which will allow us to pool resources and better coordinate on common activities, as well as to increase the impact of the work already underway within the Network. This will allow us to increase available means, enhance opportunities for work within the Network, and boost international visibility, for the benefit of all.

This first Scientific Report of the Institut Pasteur International Network is a real adventure, which must be conceptualized within the context of the Network as it exists today:

On one hand, the Network includes the Institut Pasteur, an institution that is internationally recognized for the quality and quantity of its biological research, notably on infectious diseases. As such, the Scientific Report risked reporting solely what is done in Paris, or, on the contrary, excluding Paris to better highlight the work of the rest of the Network. We have chosen an intermediate path: to describe not the totality of what is done in Paris, but the portion related to collaborations with other institutes and to the Institut Pasteur's exemplary status with regard to the Network.

On the other hand, an exhaustive reporting of activities would have resulted in an encyclopedia. For this reason, we have prioritized the most significant scientific activities, particularly those having led to publications or other forms of scientific recognition by peers. This will surely engender frustration on the part of authors of works not included in the report, and for those searching out contacts for future collaborations, but other tools are currently being designed to better respond to these needs, particularly on our website.

Written on the basis of a diverse set of documents, including annual reports, websites, articles in many different forms, and documentation sent at our request, the report was a challenge to compile. We have decided to "standardize" the presentation of the Network's activities, to ensure its readability and to properly recognize the scientific production of the Network, in a form that is usable by all its members.

YVES CHARPAK
Director of International Affairs at the Institut Pasteur

I would like to offer special thanks to Sarah Dalglish for her tenacity and thoroughness, with help from Eliane Coëffier and Isabelle Catala for the organization and execution of this report. And of course, many thanks are due to all those who took the time to reread and share their comments, a thankless but essential task.

I hope you will find this report as interesting to read as it was to compile, with the hopes that it will be but the first in a long series.

Institut Pasteur International Network

WORKING IN PARTNERSHIP

The Institut Pasteur International Network is a partnership of research and public health institutes spanning all five continents.

Born of Louis Pasteur's will to fight infectious diseases in the countries most affected by them, the Network participates in this effort via international, high-quality research.

The desire of Pasteur and that of his successors was to produce research of interest at the worldwide level while simultaneously protecting local populations. Accordingly, the training of local researchers guarantees the long-term sustainability of member institutes that are, for the most part, independent entities solidly anchored in their national contexts.

The Network is therefore a voluntary partnership, unified by common values and reinforced by numerous exchanges of ideas, personnel, knowledge, and *savoir-faire*. Thus, the Institut Pasteur International Network incarnates the words of Louis Pasteur:

"Science has no homeland; or rather science's homeland includes all of humanity."

EUROPE

Institut Pasteur, Paris France (established in 1887)

Institut Pasteur, Lille France (established in 1894)

Institut Pasteur – Fondation Cenci Bolognetti, Rome, Italy (established in 1976)

AMERICAS

Institut Pasteur in French Guiana (established in 1940)

Institut Pasteur in Guadeloupe (established in 1948)

Armand Frappier Institute (established in 1938)

Institut Pasteur in Montevideo (established in 2004)

Oswaldo Cruz Foundation (Fiocruz) established in 1900)

AFRICA

CERMES Niamey, Niger (established in 1978)

Institut Pasteur in Dakar, Senegal (established in 1923)

Institut Pasteur in Côte d'Ivoire (established in 1972)

Institut Pasteur, Bangui, Central African Republic (established in 1961)

Pasteur Center in Cameroon (established in 1959)

Institut Pasteur in Greece (established in 1919)

Cantacuzino Institute Romania (established in 1921)

Stefan Angeloff Institute, Bulgaria (established in 1947)

Institut Pasteur in Saint Petersburg, Russia (established in 1923)

Scientific Institute of Public Health, Brussels, Belgium (established in 1901)

ASIA-PACIFIC

Institut Pasteur in Cambodia (established in 1995)

Institut Pasteur in Laos (established in 2007)

National Institute of Hygiene and Epidemiology, Hanoi, Vietnam (established in 1925)

Institut Pasteur in Korea (established in 2003)

Institut Pasteur in Ho Chi Minh City (established in 1891)

Institut Pasteur in Nha Trang, Vietnam (established in 1895)

Institut Pasteur in New Caledonia (established in 1955)

Hong Kong University-Pasteur Research Center (established in 1999)

Institut Pasteur in Shanghai-Chinese Academy of Sciences (established in 2004)

MAGHREB - IRAN

Institut Pasteur in Madagascar (established in 1898)

Institut Pasteur in Morocco (established in 1929)

Institut Pasteur in Algeria (established in 1894)

Institut Pasteur in Iran (established in 1920)

Institut Pasteur in Tunis, Tunisia (established in 1893)

PART 1

PUBLIC HEALTH ACTIVITIES

One of the primary vocations of the Institut Pasteur International Network (RIIP) is to protect the health of populations in the countries where it works. RIIP member institutes perform a wide range of public health and service activities, ranging from routine childhood vaccination, to post-exposure prophylaxis for suspected rabies cases, to voluntary counselling and testing for HIV and other infections, and also including support for national health programs. In addition to these quotidian enterprises, RIIP institutes are linked into an international network that can be mobilized to respond to outbreaks and contain epidemics using the latest techniques and in partnership with worldwide bodies such as the WHO.

Surveillance & outbreak intervention

With its worldwide presence and the top-level expertise of its scientists, the RIIP is well-positioned to perform infectious disease surveillance and participate in the global response to epidemics. As such, RIIP member institutes provide technical advice at the international level, and their many National Reference Centers and WHO Centers perform regular surveillance activities of diseases with epidemic potential such as influenza, cholera, and emerging infectious diseases.

Entomological studies in Niger.

In addition, the RIIP works closely with the WHO's Global Outbreak Alert and Response Network (GOARN), which pools human and technical resources for the rapid identification, confirmation, and response to outbreaks of international importance.

Within the RIIP, member institutes react to potential epidemics in collaboration with the Laboratory for Urgent Response to Biological Threats (CIBU in the French acronym) at the Institut Pasteur. The CIBU provides:

- front-line identification of a large range of viruses and bacteria
- local or remote lab support in case of capacity surge
- networking with national and international laboratories

Under this framework, the CIBU and the RIIP have proven their capacity to respond to outbreaks. In recent years, RIIP scientists and laboratories have been involved in the response to numerous outbreaks around the globe, including:

- Yellow fever and dengue in Côte d'Ivoire
- Rift Valley fever and influenza epidemics in Madagascar
- Avian flu in Cambodia, Cameroon, and Romania
- Yellow fever in Mauritania
- Dengue fever in Paraguay
- Meningitis in Niger
- Encephalitis and influenza in Vietnam

Avian flu in Cambodia

Surveillance of emerging diseases is a top concern for RIIP scientists working in Southeast Asia, particularly regarding the H5N1 virus, responsible for avian flu. The **SISEA** and **DHHS** projects (see p. 14), coordinated by the Institut Pasteur with RIIP institutes in the region, perform active surveillance of the H5N1 virus and have responded in force to recent human cases.

Therefore, when the eighth human case of avian flu was detected by scientists at the **Institut Pasteur in Cambodia** in December 2008 during routine surveillance, Pasteur scientists immediately launched virological and epidemiological investigations.

Ninety-five close contacts of the patient, a 19-year-old man, were identified through case finding and contact tracing – none of their nasopharyngeal swabs tested positive for the H5N1 virus by PCR. In addition, scientists performed a retro-mortality study in poultry and collected environmental samples for analysis. A sero-epidemiological study was conducted among the military in December 2008 to assess the extent of viral transmission – 410 soldiers were bled and interviewed for exposure risks. The results of these investigations were still being analyzed.

Previously, scientists from the Institut Pasteur in Cambodia had performed population-based surveys to assess H5N1 seroprevalence in villages where avian influenza cases were reported in 2005-2007. Residents were interviewed on risk factors for contracting avian flu (poultry handling and food preparation practices, close contact with avian flu index cases, exposure to environmental risk factors) and blood specimens were drawn for all participants. The results showed repeated direct and close poultry contact, despite widespread knowledge of the risks of such activities (see p. 13).

Dengue fever outbreak in Côte d'Ivoire

In April 2008, an international alert was issued when surveillance activities indicated a concurrent outbreak of yellow fever and dengue-3 in Côte d'Ivoire. The dengue-3 serotype, relatively rare in Africa, has recently caused outbreaks with higher than usual incidence and severity.

Immediately, the RIIP mobilized its researchers. In Paris, the National Reference Center for Arboviruses at the **Institut Pasteur** identified dengue antibodies in specimens collected from suspected cases in travellers returning from Abidjan between May and August 2008. Further analysis by RT-PCR identified the cases as dengue-3.

The **Instituts Pasteur** in **Paris** and **Dakar** deployed a task force to transfer laboratory technology to the **Institut Pasteur** in **Côte d'Ivoire** in coordination with the WHO and the Ministry of Health. Two successive missions in September and October 2008 allowed for the creation of several diagnostic platforms and the introduction of serological tools, as well as dengue serotype-specific ELISA tests. Real-time PCR was implemented for human diagnosis and entomological investigations, and cell cultures for virus isolation were established. Finally, laboratory protocols and assays were validated on site.

Continuous exchanges between the Instituts Pasteur in Paris, Dakar, and Côte d'Ivoire are poised to sustain the capability for rapid diagnosis and confirmation of dengue virus in Côte d'Ivoire in 2009 – a partnership that will prove essential should dengue outbreaks reoccur in the region.

Vaccination and service activities

Vaccines are the most effective weapon to fight infectious disease in individuals and populations. Given their prerogative to protect public health, many institutes in the RIIP provide vaccination services or otherwise support in-country vaccination campaigns.

Vaccination center at the Institut Pasteur in Bangui.

Rabies vaccination center at the Institut Pasteur in Cambodia.

The **Instituts Pasteur in Algeria, Bangui, Cambodia, Dakar, Guadeloupe, Ho Chi Minh City, Lille, Madagascar, Morocco, Nha Trang, Tunis** and **Saint Petersburg**, as well as the **Pasteur Center in Cameroon**, all accommodate vaccination centers providing numerous essential vaccines.

The rabies vaccine is available at the **Pasteur Center in Cameroon** and at the **Instituts Pasteur in Algeria, Bangui, Cambodia, Dakar, French Guiana, Ho Chi Minh City, Iran, Madagascar, Nha Trang** and **Tunisia**. Post-exposure prophylaxis is also available at the **Scientific Institute of Public Health** in Belgium, which controls the national stock of immunoglobins.

In Paris, the **Institut Pasteur** provides routine childhood vaccination, as well as any and all vaccines necessary for international travel, including the rabies vaccine.

A number of RIIP member institutes are also involved in the production of vaccines. The **Institut Pasteur in Dakar** operates Africa's only production unit of yellow fever vaccine. The **Institut Pasteur in Ho Chi Minh City** and the **Institut Pasteur in Iran** produce the BCG and rabies vaccines. The rabies and typhoid vaccines are also produced by the **Institut Pasteur in Algeria**, which ensures the import and distribution of a number of vaccines for the Algerian population. Finally, the **Cantacuzino Institute** in Romania produces measles, influenza, tuberculosis, T and DT vaccines.

Furthermore, RIIP member institutes provide a variety of health care services to local populations, including:

- voluntary counseling and testing for HIV and hepatitis C
- a variety of medical tests (hematology, biochemistry, immuno-serology, mycobacteriology, microbiology)
- conventional and molecular diagnostic tests for bacterial and viral infections
- consultation, diagnosis, and prophylactic treatment of rabies
- food safety and environmental safety tests
- microbiological analyses of water and agricultural products
- support for national health programs against many pathologies (sexually transmitted diseases, HIV/AIDS, tuberculosis, dengue, flu, malaria...)
- occupational and school health
- vector control
- health education

Yellow fever vaccine: an expanded and renovated production unit in Dakar

The yellow fever vaccine production unit at the **Institut Pasteur in Dakar** will be expanded and renovated beginning in 2009. The Institute, which has produced the vaccine for over 70 years, currently manufactures 10 million doses annually and is one of only three producers pre-qualified by the WHO. But recent support for vaccination campaigns in Africa, notably by the GAVI Alliance, has sharply increased demand and vaccine stocks are running low.

Current plans call for production capacity to be doubled, which will require building a new facility, replacing the current lyophilisator and purchasing a second one, installing an isolation zone, and acquiring standard materials and supplies. These works are slated to begin in late 2009. When completed, the production unit should prove a potent weapon in the fight against yellow fever.

National and international technical expertise

The RIIP includes a large number of reference centers recognized for their expertise in specific areas. National Reference Centers serve as microbiological observatories for communicable diseases in the countries where they are located. WHO Collaborating Centers perform a similar function for the WHO network. Regional reference laboratories are recognized by national health ministries as competent to diagnose certain diseases.

IN THE RIIP

INSTITUTE	WHO COLLABORATING CENTERS	NATIONAL REFERENCE CENTERS RECOGNIZED BY WHO	REGIONAL REFERENCE LABORATORIES
Institut Pasteur in Algeria			Flu. Poliomyelitis. HIV/AIDS. Tuberculosis
Institut Pasteur in Bangui	Arboviruses, hemorrhagic fevers and emerging diseases. Flu. Rabies. HIV/AIDS	Flu. Poliomyelitis. Measles	Poliomyelitis
Institut Pasteur in Cambodia		Flu. Emerging infectious diseases, SARS. Arboviruses. Rabies	Avian flu (WHO). Malaria rapid diagnostic test (WHO)
Cantacuzino Institute (Romania) †	Flu	Flu. Poliomyelitis. Measles/rubella	Flu (WHO)
Institut Pasteur in Côte d'Ivoire			Avian flu (WHO)
Institut Pasteur in Dakar	Arboviruses and hemorrhagic fevers	Flu. Poliovirus. Measles	Avian flu (WHO)
Pasteur Center in Cameroon		Avian flu (WHO)	Avian flu (WHO)
NIHE (Vietnam)	Occupational health	Flu. Poliomyelitis	
Institut Pasteur in French Guiana		Arboviruses and *Influenzae* viruses.* Malaria chemoresistance*	
Institut Pasteur in Greece		Flu. Poliomyelitis. Measles/rubella. Avian flu	Leishmaniasis. *Neisseria gonorrheae*
Institut Pasteur in Iran	Rabies	Arboviruses and hemorrhagic fevers	
Institut Pasteur in Madagascar	Plague	Flu. Avian flu. Poliomyelitis. Measles	Avian flu (WHO)
Institut Pasteur in New Caledonia		Flu	Regional observatory for pneumococcus
Institut Pasteur in Tunis	Leishmaniasis	Poliovirus (WHO)	Poliovirus. Measles. Papillomavirus
Institut Pasteur in Saint Petersburg		Avian flu. Emerging infectious diseases, SARS	
Scientific Institute for Public Health (Belgium)		Flu. Avian flu. Measles. Rubella. Rabies. Viral hepatitis	SARS. West Nile virus. Bacterial encephalitis. Botulism. Foodborne outbreaks and microbiology. Listeriosis. Medical mycology. Salmonella. Shigella. Tuberculosis and mycobacteria. Toxoplasmosis.

* in the Antilles-Guiana region.
† designated by the ECDC (European Center for Disease Prevention and Control) as a competent body for surveillance, response, and scientific advice.

AT THE INSTITUT PASTEUR

NATIONAL REFERENCE CENTERS
Anaerobic bacteria and botulism
Anthrax
Arboviruses
Arboviruses and *Influenzae* viruses (Antilles-Guiana region)
Borrelia
Chemoresistance for malaria (Antilles-Guiana region)
Escherichia coli and Shigella
Human papillomavirus
Influenzae viruses, northern France
Leptospirosis
Listeria
Meningococcus
Mycology and anti-fungals
Pertussis and other Bordetella
Plague and other yersinoses
Rabies
Resistance to antibiotics
Salmonella
Toxicogenomic corynebacteria
Vibrions and cholera
Viral hemorrhagic fevers

WHO COLLABORATING CENTERS
Enterovirus and viral vaccines
Epidemiology of leptospirosis
Flu viruses and other respiratory viruses
Foodborne listeriosis
Rabies
Salmonellae
Viral hemorrhagic fevers
Yersinia

Isolating strains of *Listeria monocytogenes*, a foodborne pathogen, at the National Reference Center for Listeria at the Institut Pasteur.
© *Institut Pasteur*

PART 2

RESEARCH ON INFECTIOUS DISEASES

The RIIP is at the forefront of knowledge on infectious diseases, performing research that is both international, linking teams working oceans away, and multi-disciplinary. RIIP research projects may include epidemiologists, virologists, immunologists, entomologists and many others, who work together to fight pathogens both inside and outside their human hosts.

To learn more about research on diseases at the Institut Pasteur – too extensive to be detailed here – visit:
www.pasteur.fr

HIV / AIDS

The RIIP is involved in numerous research projects on HIV/AIDS and its co-infections, particularly in Africa and Southeast Asia, the two regions most affected by the epidemic. This work relates to epidemiological and biomedical aspects of the disease, as well as the development of new antiviral agents.

SURVEILLANCE AND PUBLIC HEALTH

The **Instituts Pasteur in Algeria, Madagascar, Ho Chi Minh City** and **Saint Petersburg** conducted epidemiological studies in their respective regions, including enquiries on the biodiversity of HIV strains. Many institutes in the RIIP shared their epidemiological expertise with neighboring countries. A prime example is the **Institut Pasteur in Madagascar**, which has studied the biodiversity of HIV strains in the Seychelles.

The **Institut Pasteur in Cambodia** implemented a real-time quantitative PCR testing technique with support from the ANRS (French National Agency for Research on AIDS and viral hepatitis). This approach enables early diagnosis of HIV-positive neonates. For children who live in regions far removed from diagnostic centers, the possibility of using blotting paper to perform these tests is currently being studied.

Nobel Prize

The 2008 Nobel Prize in Medicine was awarded to Professors Françoise Barré-Sinoussi and Luc Montagnier of the **Institut Pasteur** for their work leading to the discovery of the AIDS virus in January 1983.

NATURAL FACTORS OF PROTECTION

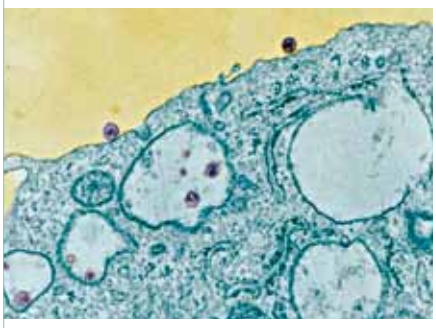
Researchers from the **Institut Pasteur in Bangui** compared two HIV-negative populations: one at high risk of infection (unprotected partners of HIV-positive individuals) and one at low risk (blood donors). They concluded that weaker activation of T CD4 + lymphocytes may protect against HIV infection in group of HIV-negative partners[1].

The **Institut Pasteur in Cambodia** conducted an ANRS-funded study on a cohort of patients at high risk of infection, compared with a cohort of patients who had not been exposed to HIV. The results suggest that HIV-specific humoral immune cells might protect against infection[2].

In collaboration with numerous francophone partners, the **Institut Pasteur in Lille** analyzed the genomes of a cohort of 275 HIV non-progressors. This study allowed researchers to identify a new, isolated mutation which seems to protect against disease progression[3].

IN 2008

- ☐ analysis of the etiology of sputum-negative pneumonia in HIV-positive patients in Africa and Asia
- ☐ identification of multiple natural factors of protection against HIV infection
- ☐ proof of the increased risk of mother-to-child HIV transmission in women infected with *P. falciparum* in Cameroon
- ☐ demonstration of the role of natural killer (NK) cells in inflammation related to immune reconstitution syndrome at the Institut Pasteur (Paris)



Entry of HIV-1 into a macrophage. Two viral particles linked to the surface of the cell are ready to fuse with the cellular membrane to accomplish entry. Colorized image.
© Prévost, M.-C. ; Schwartz, O. / Institut Pasteur

(1) Bégaud E et al. "Reduced CD4 T cell activation and in vitro susceptibility to HIV-1 infection in exposed uninfected Central Africans." *Retrovirology.* 2006 Jun 22; 3: 35.
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(3) Limou S et al. "Genomewide Association Study of an AIDS-Nonprogression Cohort Emphasizes the Role Played by HLA Genes (ANRS Genomewide Association Study 02)." *J Infect Dis.* 2008 Dec 30 [Epub ahead of print].
(4) Scott-Algara D et al. "The CD85j+ NK cell subset potently controls HIV-1 replication in autologous dendritic cells." *PLoS ONE.* 2008 Apr 9; 3(4): e1975.
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X-ray of pneumocystosis in an HIV-positive patient. Compared to a normal patient, it is whiter.
© Trotot, P. / Institut Pasteur

CO-INFECTIONS

The **Institut Pasteur in Cambodia** implemented two studies on HIV/tuberculosis co-infection. The **CAMELIA** clinical study (CAMbodia Early vs. Late Introduction of Antiretroviral therapy), financed by the ANRS and realized in partnership with the NIH, aims to identify the opportune moment for beginning anti-retroviral treatment in patients who are severely immunocompromised and undergoing treatment for tuberculosis. In parallel, Françoise Barré-Sinoussi's team at the **Institut Pasteur** is studying innate NK response during the onset of inflammatory syndromes related to immune system reconstitution[4].

A multi-site cohort study (Phnom Penh, Ho Chi Minh City, Bangui and Dakar) analyzed the etiology of sputum-negative pneumonia in HIV-positive patients and showed that its causes differ in Africa and Asia[5].

MOTHER-TO-CHILD TRANSMISSION

Studies on the prevention of mother-to-child HIV transmission have shown that pregnant women infected with *P. falciparum*, the parasite that causes malaria, are more likely to transmit HIV to their children[6]. The analysis, completed by the **Institut Pasteur** and the **Pasteur Center in Cameroon**, emphasizes the need to provide malaria prophylaxis for HIV-positive pregnant women.

In a phase II clinical study, the **Instituts Pasteur in Cambodia** and **Côte d'Ivoire** are analyzing the effectiveness of Truvada® as an alternative to Nevirapine in preventing mother-to-child HIV transmission[7].

BASIC RESEARCH

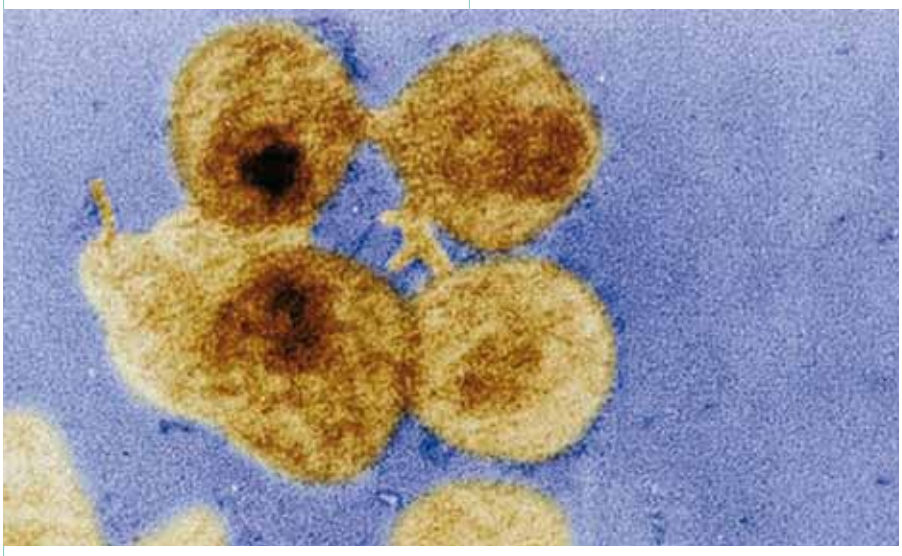
New anti-HIV agents are being studied in various laboratories, notably at the **Institut Pasteur–Cenci Bolognetti Foundation**, where a team is working to develop new reverse-transcriptase[8] and integrase inhibitors[9].

The **HKU–Pasteur Research Center** uses systematic screening techniques to identify post-entry HIV-1 inhibitors, as well as approaches that enable the identification of new medicines capable of changing the phenotype of a cell infected with HIV-1[10]. The **Institut Pasteur in Korea** is using a high-volume screening platform to identify medications with identical targets.

Along these same lines, the **Institut Pasteur in Shanghai** is attempting to strengthen the surfaces of HIV-1 target cells to make them more infection-resistant *in vitro*. Another team is studying the interactions between HIV-1 and Human Herpes Virus 8 (HHV-8), which causes Kaposi's sarcoma and is frequently associated with HIV-1 infection. Several approaches are tested to improve anti-HIV humoral and mucosal immune responses.

CLINICAL RESEARCH

Scientists from the **Pasteur Center in Cameroon** are working in cooperation with the **Instituts Pasteur in Dakar** and **Bangui** and the **Institut Pasteur** on the ANRS-funded "Pediacam" project, which studies the joint impact of routine vaccination and triple therapy on HIV-infected infants. After vaccination under the WHO's Expanded Program on Immunization (EPI), HIV-positive children were found to have lower antibody levels than HIV-negative children. Measles antibody levels were particularly low in severely immunocompromised children[11].



Viral particles of HIV-1, causal agent of AIDS. Colorized image.
© Montagnier, L. / Institut Pasteur

(6) Ayouba A, et al. "Specific stimulation of HIV-1 replication in human placental trophoblasts by an antigen of *Plasmodium* falciparum." *AIDS.* 2008 Mar 30; 22(6): 785-7.
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(11) Tejiokem MC et al. "HIV-infected children living in Central Africa have low persistence of antibodies to vaccines used in the Expanded Program on Immunization." *PLoS ONE.* 2007 Dec 5; 2(12): e1260.

Hepatitis

At least eight hepatitis viruses (A-G) are currently known to science, causing pathologies of varying degrees of seriousness. Of these, the hepatitis B virus (HBV) is one of the most widespread viruses in the world: approximately 2 billion people have been exposed through pathways that are still poorly understood. The other hepatitis viruses are less widespread but can also result in sometimes-lethal complications, as is notably the case with the hepatitis C virus (HCV).

IN 2008

- ☐ demonstration of near-universal HAV exposure in children over 10 years old in Madagascar
- ☐ survey of nosocomial and sexual HGV transmission in Iran
- ☐ explanation of molecular mechanisms of HCV infection at the Institut Pasteur in Lille

SURVEILLANCE AND PUBLIC HEALTH

The **Institut Pasteur in Iran** found a relatively high HGV infection rate (11%) in HIV-positive patients, especially among those who were intravenous drug users[1].

The **Institut Pasteur in Madagascar** found almost universal HAV exposure in subjects over 10 years old in Antananarivo, despite improvements in the city's sanitation conditions[2]. These researchers also demonstrated that most HCV infections are acquired in hospitals[3]. Finally, they evaluated the performance of four HBV diagnostic kits[4].

Researchers at the **Institut Pasteur in Morocco** demonstrated the predominance of the HBV genotype D in that country[5]. The genetic diversity of HCV is still being studied.

GENETIC AND MOLECULAR STUDIES

Researchers at the **Pasteur Center in Cameroon** used a new method (Bayesian evolutionary analysis) to prove that the HCV-2 strains found in Cameroon originated in West Africa[6].

At the **Institut Pasteur in Bangui**, researchers sequenced HBV strains and discovered that genotype E is predominant in Central African Republic, rather than East African strains[7].

DIAGNOSIS, TREATMENT, VACCINE

A research project uniting the **Instituts Pasteur in Greece**, **Ho Chi Minh City, Iran, Paris,** and **Saint Petersburg,** as well as the **Cantacuzino Institute** in Romania, highlighted a link between the genetic diversity of HCV and difficulties related to diagnosis. These studies have opened new pathways toward the development of a vaccine.

An collaborative project involving the **Institut Pasteur**, the **Pasteur Center in Cameroon,** and the **Instituts Pasteur in Dakar** and **Bangui**, seeks to identify markers for early childhood HBV infection in Senegal, Cameroon and the Central African Republic.

BASIC RESEARCH

Researchers at the **Institut Pasteur in Lille** published results on the molecular mechanisms for entry, replication and assembly of the HCV virus in the host cell[8].

The **Institut Pasteur-Cenci Bolognetti Foundation** is developing bioinformatic tools for HCV protein structures and the analysis of variability in the viral genome.
Researchers at the **Institut Pasteur in Greece** identified a new HCV viral protein called core+1, which may be involved in interaction with the host cell[9].

CLINICAL RESEARCH

The **Institut Pasteur in Dakar** is participating in a clinical study funded by the ANRS to evaluate the effectiveness of treating chronic hepatitis B carriers with a combination of antivirals (lamivudine) and a vaccine.

In Casablanca, researchers from **Institut Pasteur in Morocco** are studying genetic predispositions to HBV and HCV infection. They are also looking at the risks of developing cirrhosis and liver cancer[10].

A project involving the **Instituts Pasteur in Morocco, Algeria** and **Tunis** and the **Institut Pasteur** examined the etiology of hepatocellular carcinoma in North Africa, as well as the genetic mechanisms involved in carcinogenesis.

Viral hepatitis in Egypt

Researchers at the **Institut Pasteur** are conducting a project funded by the ANRS on viral hepatitis in Egypt, where HCV prevalence rates are among the highest in the world. In 2008, the primary outcomes were:

- ☐ a new method for predicting the effectiveness of HCV treatments[11]
- ☐ apparent proof of intra-familial transmission of HCV[12]

(1) Ramezan A et al. "Frequency of hepatitis G virus infection among HIV positive subjects with parenteral and sexual exposure." *J Gastrointestin Liver Dis.* 2008 Sept; 17(3): 269-72.
(2) Raharimanga V et al. "Age-specific seroprevalence of hepatitis A in Antananarivo (Madagascar)." *BMC Infect Dis.* 2008 Jun 6; 8:78.
(3) Ramarokoto CE et al. "Seroprevalence of hepatitis C and associated risk factors in urban areas of Antananarivo, Madagascar." *BMC Infect Dis.* 2008 Feb 29; 8:25.
(4) Randrianirina F et al. "Evaluation of the performance of four rapid tests for detection of hepatitis B surface antigen in Antananarivo, Madagascar." *J Virol Methods.* 2008 Aug; 151(2):294-7. Epub 2008 May 6
(5) Ezzikouri S et al. "Genotype determination in Moroccan hepatitis B chronic carriers." *Infect Genet Evol.* 2008 May;8(3):306-12. Epub 2008 Feb 3.
(6) Pouillot R et al. "Variable epidemic histories of hepatitis C virus genotype 2 infection in West Africa and Cameroon." *Infect Genet Evol.* 2008 Sep; 8(5):676-81.
(7) Bekondi C et al. "Central African Republic is part of the West-African hepatitis B virus genotype E crescent." *J Clin Virol.* 2007 Sep; 40(1): 31,7.
(8) Rocha-Perugini V et al. "The CD81 partner EWI-2wint inhibits hepatitis C virus entry." *PLoS ONE.* 2008 Apr 2; 3(4): e1866.
(9) Vassilaki N et al. "Expression studies of the HCV-1a core+1 open reading frame in mammalian cells." *Virus Res.* 2008 May; 133(2):123-35.
(10) Ezzikouri S et al. "The Pro variant of the p53 codon 72 polymorphism is associated with hepatocellular carcinoma in Moroccan population." *Hepatol Res.* 2007 Sep; 37(9): 748-54.
(11) Abdoul H et al. "Serum alphfa-fetoprotein predicts treatment outcome in chronic hepatitis C patients regardless of HCV genotype." *PLoS ONE.* 2008 Jun 11; 3(6): e2391.
(12) Plancoulaine S et al. "Dissection of familial correlations in hepatitis C virus (HCV) seroprevalence suggests intrafamilial viral transmission and genetic predisposition to infection." *Gut.* 2008 Sep; 57(9): 1268-74.

Influenza

Surveillance of influenza viruses and prevention of their transmission is essential to controlling seasonal flu outbreaks and containing potential pandemics. The RIIP is heavily involved in these efforts, with sentinel sites and regular laboratory monitoring, and is participating in the preparation of a rapid and effective response plan in the event of flu virus outbreaks.

IN 2008

- ☐ work on the immune and inflammatory respone to influenza A by the Institut Pasteur
- ☐ studies on the presence of the H5N1 virus in Cambodia
- ☐ first identification of the H5N1 virus in Cameroon
- ☐ efforts to develop a more sensitive diagnostic tool for avian flu, carried out by various RIIP institutes in Asia

SURVEILLANCE AND PUBLIC HEALTH

Thirteen RIIP institutes conduct regular surveillance activities based on clinical, epidemiological, and virological data as members of the WHO Global Influenza Surveillance Network (see map). Some centers also monitor abnormal mortality in wild or domestic birds in order to follow the spread of the H5N1 virus. Their virological expertise in this matter has been recognized by the WHO.

For influenza, the **Institut Pasteur in Madagascar** maintains one of the region's largest flu surveillance networks. Also, researchers at the **Institut Pasteur in Côte d'Ivoire** have shown that 73% of recent human cases were caused by the type A influenza virus and the others were caused by the type B virus[1].

Regarding avian flu, the **Pasteur Center in Cameroon** analyzed samples taken from sick or dead birds and identified (non-human) cases of highly pathogenic avian flu in Cameroon[2]. In Central African Republic, researchers at the **Institut Pasteur in Bangui** are working with veterinarians to perform surveillance in poultry populations.

EPIDEMIOLOGY

Researchers at the **Instituts Pasteur in Dakar, Madagascar** and **Côte d'Ivoire** as well as at the **Pasteur Center in Cameroon** and the **CERMES** in Niger are working to identify the prevalence and seasonality of flu viruses in humans. This information will enable the creation of a serum and virus data-bank, allowing for a better understanding of the epidemiology and ecology of flu viruses.

Researchers at the **Institut Pasteur in Cambodia** published a study identifying modes of transmission for the H5N1 virus by analyzing an epidemic in a Cambodian village[3]. Also in Cambodia, studies on the frequency and patterns of contact with poultry shed light on the risk of transmission to humans[4]. Moreover, the **BSL-3 laboratory** at the **Institut Pasteur in Cambodia** allows for in-depth virological research on these topics.

DIAGNOSIS, TREATMENT, VACCINE

The unit on emerging viruses at the **Institut Pasteur in Shanghai** is collaborating with the **HKU-Pasteur Research Center** and the **Institut Pasteur in Cambodia** to develop and evaluate a diagnostic test for avian flu that is more sensitive than existing tests[5]. In addition, researchers in Hong Kong have developed a method for serodiagnosis of the H5N1 virus based on the use of lentiviruses, which does not require a BSL-3 laboratory[6].

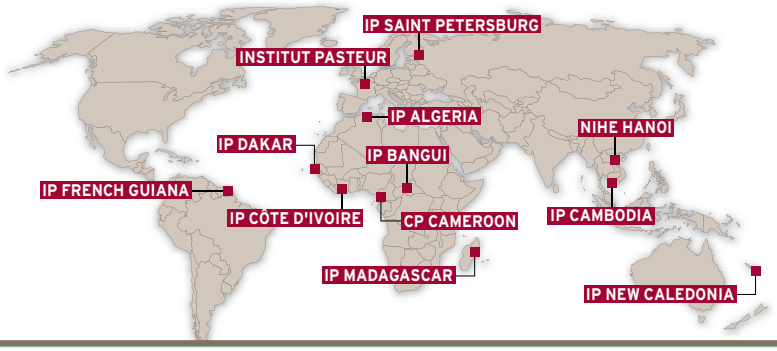
BASIC RESEARCH

Researchers at the **Institut Pasteur in Cambodia** have described the entire genome of nearly 40 H5N1 viral strains identified since 2004, which they then made available to the WHO, as well as to the international community of avian influenza experts[7].

Another study in Cambodia described the virus' presence in the environment (in mud, topsoil, aquatic plants, etc.), suggesting the need to disinfect poultry-raising facilities[8].
The **Institut Pasteur in Korea** is performing molecular screening to identify therapeutic targets for combating influenza.

WHO Global Influenza Surveillance Network

Influenza surveillance and identification of H5N1 virus



(1) Akoua-Koffi C et al. "[Results of two-year surveillance of flu in Abidjan, Côte d'Ivoire]." *Med Trop (Mars).* 2007 Jun; 67(3):259-62.
(2) Richard Njouom et al. "Highly pathogenic avian influenza virus subtype H5N1 in ducks in the Northern part of Cameroon." *Veterinary Microbiology.* 2008; 130: 380-4.
(3) Vong S et al. "Low frequency of poultry-to-human H5NI virus transmission, southern Cambodia, 2005." *Emerg Infect Dis.* 2006 Oct;12(10):1542-7.
(4) Ly S et al. "Interaction between humans and poultry, rural Cambodia." *Emerg Infect Dis.* 2007 Jan;13(1):130-2.
(5) Wang W et al. "Design of multiplexed detection assays for the diagnosis of human pathogenic avian influenza A subtypes by SmartCycler real-time reverse transcription-PCR." *J Clin Micrbiol.* 2008 Oct 29 [Epub].
(6) Nefkens I et al. Hemagglutinin pseudotyped lentivriral particles: characterization of a new method for avian H5N1 influenza sero-diagnosis." *J Clin Virol.* 2007 May; 39(1): 27-33.
(7) Buchy P et al. "Influenza A/H5N1 virus infection in humans in Cambodia." *J Clin Virol.* 2007 Juli 39(3): 164-8.
(8) Vong S et al. "Environmental contamination during influenza A virus (H5N1) outbreaks, Cambodia, 2006." *Emerg Infect Dis.* 2008 Aug; 14(8):1303-5.

At the **Institut Pasteur**, researchers at the Innate Host Defense and Inflammation Unit studied immune response and inflammation regulation in the presence of the influenza A virus[9]. Another study examined the role of proteases and antiproteases in pulmonary inflammation caused by the influenza A virus[10]. In the Molecular Genetics of Respiratory Viruses unit, researchers identified cellular and viral factors that limit replication of type A influenza viruses in humans[11].

Finally, the **HKU-Pasteur Research Center** has identified cellulars factors that interact with structural proteins of the H5N1 virus. It is part of the Hong-Kong Area of Excellence on the "Control of Pandemic and Inter-Pandemic Influenza".

IMMUNOLOGY

The Molecular Virology Unit at the **Institut Pasteur in Shanghai** is studying the suppression of virus entry mechanisms as a potential therapeutic target. Another team is developing lentivirus vectors for the purpose of finding an effective vaccine against the H5N1 virus. This work led to the filing of a patent on lentivirus vectors in 2008. A third project aims to identify the *in vivo* tolerance and immune response of T lymphocytes during infection by an influenza virus, as well as their potential use in immunotherapy.

Researchers at the **HKU-Pasteur Research Center** are currently studying innate and acquired immune responses against seasonal and pandemic influenza A viruses with an approach at the interface between basic and applied research.

In Romania, researchers at the **Cantacuzino Institute** are conducting a project to evaluate immunogenicity in mice that are exposed to a H5N1 vaccine candidate.

Finally, the **Armand Frappier Institute** in Canada demonstrated that immune response and symptoms in ferrets exposed to influenza viruses varies depending on the virus sub-type[12].

International influenza projects

The RIIP is involved in many large international projects on the influenza viruses. A few highlights are:

☐ **"Support, training and capability enhancement," funded by the United States Department of Health and Human Services (DHHS) (2006-2009)**
The goal of this project is to strengthen influenza surveillance networks in Africa and Southeast Asia, particularly as they relate to avian flu, as well as to conduct epidemiological studies on these diseases. To fulfill these objectives, the DHHS program has implemented customized training sessions on performing investigations in the event of an animal epidemic.
Participating institutes: the Instituts Pasteur in Cambodia, Ho Chi Minh City, Nha Trang, Laos, Côte d'Ivoire, Dakar, Bangui and Madagascar, as well as the NIHE in Hanoi and the Pasteur Center in Cameroon.

☐ **"Strengthening the Influenza Surveillance Network in Africa," funded by the French Ministry of Health (2006-2009)**
This project functions in concert with the DHHS program in Africa. Its main activities concern the detection and characterization of influenza viruses, as well as laboratory improvements. In addition, the project subsidizes a cross-disciplinary study on the typology of influenza strains circulating in sub-Saharan Africa, in order to better understand transmission pathways.
This program also finances the construction of a BSL-3 laboratory in Bangui (Central African Republic), to be inaugurated in 2009.
Participating institutes: the Instituts Pasteur in Bangui, Côte d'Ivoire, Dakar, and Madagascar; the Pasteur Center in Cameroon; and the CERMES (Niger).

☐ **SISEA (Surveillance and Investigation of Endemic Situations in Southeast Asia) (2006-2009)**
The goal of SISEA, a project funded by the French Development Agency (AFD), is to improve detection and management of emerging diseases, including avian influenza, in Southeast Asia. The project relies on WHO reference laboratories within the RIIP, which coordinate epidemiological surveillance of emerging viruses. The project has three key components: improvement of diagnostic capabilities at reference laboratories and making these more widely available in the network, rationalization of national surveillance systems, and coordination at the national and regional level, notably with the WHO, the OIE and the FAO.
Participating institutes: the Instituts Pasteur in Cambodia, Ho Chi Minh City, Nha Trang, and Shanghai; the NIHE in Vietnam; and the NCLE in Laos

☐ **RIVERS: "Resistance of Influenza Viruses in Environmental Reservoirs and Systems" (FP-6) (2007-2010)**
The RIVERS project aims for a better understanding of the survival mechanisms of influenza viruses in the environment. Participating institutes are studying the role of reservoirs in the transmission of the H5N1 virus with the goal of proposing standardized protocols for detecting these viruses in food and water. Other studies focus on the impact of water treatments on virus survival in order to identify optimal pH, salinity and water temperature and propose appropriate chemical treatments.
Participating institutes: the Cantacuzino Institute (Romania), the Stephan Angeloff Institute (Bulgaria), and the Instituts Pasteur in Cambodia, Shanghai and Lille.

(9) Pothlichet J et al. "Cutting edge: innate immune response triggered by influenza A virus is negatively regulated by SOCS1 and SOCS3 through a RIG-I/IFNAR1-dependent pathway." *J Immunol.* 2008 Feb 15; 180(4): 2034-8.
(10) Barbier D et al. "Implication of proteases and anti-proteases during IAV infection and pulmonary inflammation." *Rev Mal Respir.* 2008 Nov; 25(9):1185
(11) Rameix-Welti MA et al. "Avian influenza A polymerase association with nucleoprotein, but not polymerase assembly, is impaired in human cells during the course of infection." *J Virol.* 2008 Nov. 19 [EPub].
(12) Svitek N et al. "Severe seasonal influenza in ferrets correlates with reduced interferon and increased IL-6 induction." *Virology.* 2008 Jun 30; 376(1): 53-9.

Dengue fever

Dengue fever is caused by four viruses that are transmitted to humans primarily by the Aedes aegypti *mosquito. Each year, between 60 and 100 million people are infected, primarily in Southeast Asia and Latin America, and more than 20 million people die from serious forms of the disease, particularly the hemorrhagic form. Most of these deaths involve children younger than 15 years of age. At present, there is no vaccine or specific treatment.*

IN 2008

- ☐ detection of cases of dengue-3 in Côte d'Ivoire and sylvan dengue-2 in Mali and Senegal
- ☐ evaluation of diagnostic tools based on detection of the NS1 antigen, a collaboration between French Guiana, Dakar and Paris
- ☐ identification of 13 species of forest-dwelling mammals in South America that are susceptible to infection with the dengue viruses

Mosquito nets protect aganinst and other mosquito-borne diseases.

SURVEILLANCE AND PUBLIC HEALTH

The National Reference Center for Arboviruses at the **Institut Pasteur** isolated and sequenced strains of sylvan dengue-2 which were responsible for an epidemic in Mali, an investigation that was launched at the request of the WHO's Global Outbreak and Response Network (GOARN). The Center also worked with the **Instituts Pasteur in Côte d'Ivoire** and **Dakar** to respond to a dengue-3 outbreak in Abidjan.

In addition, the **Institut Pasteur in New Caledonia** confirmed the existence of dengue-4 on the archipelago, as well as a dengue-1 epidemic in 2008.

Finally, researchers from the **Institut Pasteur in French Guiana** confirmed the concomitant circulation of the dengue-2 and dengue-3 serotypes during an epidemic in Paraguay[1]. This institute also houses a National Reference Center for Arboviruses for the Antilles-Guiana region, and participates in surveillance of dengue serotypes circulating in Guiana, Martinique and Guadeloupe. In 2008, surveillance expanded to the islands of Saint Martin and Saint Barts thanks to the technique of gathering biological samples on blotting paper.

In Africa and Asia, dengue has a forest-based life cycle involving non-human primates. In contrast, there are no known animal reservoirs in South America, though infection has been documented in small mammals on the outskirts of Cayenne[5]. A project uniting the **Instituts Pasteur in French Guiana** and **Dakar** has been launched to identify the virus' circulation in wild mammals in Guiana and Senegal. This project will also examine the role of sylvan mosquitoes other than *Aedes aegypti* as vectors or potential reservoirs.

DIAGNOSIS, TREATMENT, VACCINE

The **Instituts Pasteur in French Guiana** and **Dakar**, in collaboration with the Institut Pasteur, evaluated diagnostic tools based on the detection of the NS1 antigen in patients in the early stages of the disease[2].

The **Institut Pasteur in New Caledonia** studied the causes of false positive results in two diagnostic tests for dengue fever[3].

A study aimed at identifying the precise incidence of dengue is currently being performed on a cohort of 10,000 participants by the **Institut Pasteur in Cambodia**, with the goal of precisely identifying the incidence of dengue and serotyping dengue viruses using PCR. This project is financed by the Pediatric Dengue Vaccine Initiative (PDVI). Another project, performed in collaboration with the Cambodian armed services, seeks to identify mechanisms of blood loss in the course of dengue infection with the aim of discovering new therapeutic targets.

(1) Matheus S. "Dengue-3 outbreak in Paraguay: investigations using capillary blood samples on filter paper." *Am J Trop Med Hyg.* 2008 No; 79(5): 685-7.
(2) Dussart S et al. "Evaluation of two new commercial tests for the diagnosis of acute dengue virus infection using NS1 antigen detection in human serum." *PLoS Negl Trop Dis.* 2008 Aug 20; 2(8); e280.
(3) Berlioz-Arthaud A et al. "Comparison of PanBio dengue IgM ELISA assay with pentax dengue IgM particle agglutination assay to evaluate factors affecting false positive results." *Southeast Asian J Trop Med Public Health.* 2008 Jan; 39(1): 55-61.
(4) Wing WH et al. "Dermal-type macrophages expressing CD209/DC-SIGN show inherent resistance to dengue virus growth." *PLoS Negl Trop Dis.* 2008 Oct 1; 2(10): e311.
(5) Thoisy BD et al. "Dengue infection in neotropical forest animals." *Vector Borne Zoonotic Dis.* 2008 Oct 22. [Epub ahead of print].

Denframe: Improving dengue diagnosis

The **Denframe** project, financed by the European Union, unites 13 laboratories including five institutes in the RIIP: the **Instituts Pasteur in Cambodia, Ho Chi Minh City** and **French Guiana**, the **HKU-Pasteur Research Center** and the **Institut Pasteur**.
The Denframe project has two main objectives:

☐ Standardization of diagnostic methods and development of new diagnostic tools.

☐ Development of new therapeutic approaches based on studies of host-pathogen interactions and specifically on the innate immune response caused by infection.

Numerous scientific activities are currently underway:

☐ A clinical cohort study at four sites **(Cambodia, Vietnam, Brazil, French Guiana)** aims to determine the proportion of asymptomatic infections and infection rates within households, to compare clinical and biological data, and to establish the sensitivity of the PlateliaTM diagnostic test.

☐ Researchers at the **Institut Pasteur in Cambodia** are studying the first stages of anti-dengue immunity by comparing two cohorts, one which is symptomatic and another which is asymptomatic.

Avian influenza module of the BSL-3 laboratory at the Institut Pasteur in Cambodia.

☐ The **Institut Pasteur** has developed new serological tests for flavivirus infections in collaboration with the **Institut Pasteur** in **French Guiana**. These tests, specific to each dengue serotype, have been evaluated as appropriate reagents for the early detection of IgMs.

☐ The **HKU-Pasteur Center's** screening platform, in collaboration with the University College of London and Shanghai Institute for Materia Medica, concluded a preliminary screening for dengue virus replication inhibitors. Some 20 potential inhibitors were identified. Also being studied are dengue virus-like particles, used to identify cellular machineries involved in assembly and budding of dengue virus in mammalian cells.

☐ The **Institut Pasteur** is studying the genetic elements of sensitivity to the dengue virus based on genes involved in innate antiviral immunity.

Aedes albopictus is one of the vectors of the dengue and Chikungunya viruses. In Reunion, it has spread thanks to its ecological flexibility, since it can colonize both urban and forest zones.
© Anna-Bella Failloux-Manuellan / Service photo / Institut Pasteur

Finally, researchers from various units at the **Institut Pasteur** continue to collaborate on a dengue vaccine candidate in the context of the MVDVax program.

IMMUNOLOGY

The unit on Flavivirus-Host Molecular Interactions at the **Institut Pasteur** highlighted a new mechanism of resistance to the dengue virus, which might lead to new strategies for preventing this disease[4].

ENTOMOLOGY

A collaborative project is studying the vectoral capabilities of the *Aedes aegypti* mosquito and risk factors for the transmission of dengue viruses. This project involves the **Instituts Pasteur in French Guiana** and **Guadeloupe** as well as the Institut Pasteur. In this context, researchers are seeking to identify the bio-ecology of *Aedes aegypti* in the Antilles-Guiana region. In Guiana, studies are also being carried out on the effectiveness of insecticides used in vector control activities.

At the **Institut Pasteur in Dakar**, researchers are studying changes in the viral genome caused by passage through the *Aedes aegypti* mosquito.

To learn more about research on diseases at the Institut Pasteur – too extensive to be detailed here – visit:
www.pasteur.fr

Chikungunya

The first epidemic caused by the Chikungunya arbovirus occurred in Tanzania in 1952, but it was the Indian Ocean epidemic of 2005-2006 that brought this disease to the world's attention. A relative of the dengue viruses, the Chikungunya virus causes severe joint pain and can be fatal in vulnerable patients.

IN 2008

- ☐ new description of the replication of the strain responsible for the Indian Ocean epidemic of 2005-2006
- ☐ identification of potential virus inhibitors at the Institut Pasteur
- ☐ development of an animal model at the Institut Pasteur

SURVEILLANCE AND PUBLIC HEALTH

Researchers at the **Institut Pasteur** described the replication of the Chikungunya virus strains involved in the 2005-2006 epidemic on Reunion Island[1]. In-depth studies of the genomes of the six viral isolates have provided a better understanding of the virulence of these strains[2].

In addition, teams of RIIP researchers were mobilized multiple times in 2008 to confirm the existence of the Chikungunya virus in Africa. In France, the National Reference Center for Arboviruses is a key player in Chikungunya surveillance and in the mandatory reporting of this disease.

DIAGNOSIS, TREATMENT, VACCINE

Researchers from the **Institut Pasteur** and the **Institut Pasteur in Dakar** have, in partnership with the Biorad corporation, developed the first monoclonal antibodies specific to the Chikungunya virus, as well as a viral antigen for serological tests[3].

Researchers from the **Institut Pasteur in Dakar** are currently evaluating for approval a method of molecular diagnosis for Chikungunya virus strains circulating in West Africa.

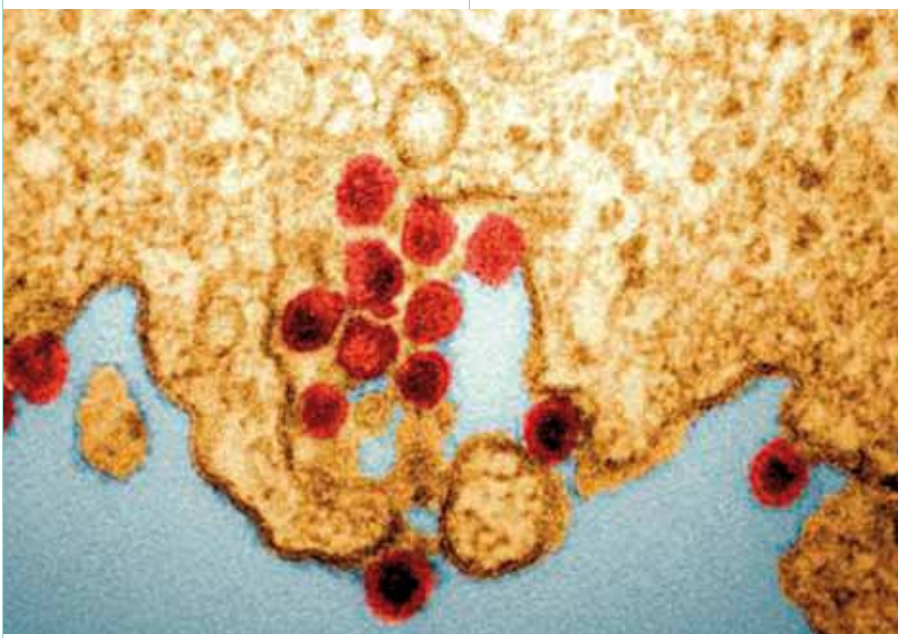
ENTOMOLOGY

In a collaborative project, the **Pasteur Center in Cameroon** and the **Institut Pasteur in Madagascar** are studying the biodiversity, phylogeography and evolutionary dynamic of mosquitoes that are vectors for Chikungunya and other mosquito-borne fevers.

In addition, researchers at the **Institut Pasteur** have shown that there are two types of infection in the *Aedes albopictus* mosquito[4].

BASIC RESEARCH

Researchers from the **Institut Pasteur** have created an animal model (young wild-type mice) for Chikungunya, a development that will facilitate the search for new vaccines and treatments[5]. Another Paris-based team has found clues regarding potential inhibitors in the course of research on the E2 glycoprotein in human muscle tissue[6]. Finally, a molecular inhibitor for the Chikungunya virus has been recently identified in humans[7].



Human cell infected by the Chikungunya virus. The virus is round; it can be distinguished by its capsid (a sort of shell) surrounded by an envelope. Colorized image.
© M. Sourisseau - M. C. Prévost - O. Schwartz / Institut Pasteur

(1) Sourisseau M et al. "Characterization of reemerging chikungunya virus." *PLoS Pathog.* 2007 Jun; 3(6): e89.
(2) Schuffenecker I et al. "Genome microevolution of chikungunya viruses causing the Indian Ocean outbreak." *PLoS Med.* 2006 Jul; 3(7):e263.
(3) Bréhin AC et al. "Production and characterization of mouse monoclonal antibodies reactive to Chikungunya envelope E2 glycoprotein." *Virology.* 2008 Feb 5; 371(1): 185-95.
(4) Vazeille M et al. "Two Chikungunya isolates from the outbreak of La Reunion (Indian Ocean) exhibit different patterns of infection in the mosquito, Aedes albopictus." *PLoS ONE.* 2007 Nov 14; 2(11):e1168.
(5) Couderc T. A mouse model for Chikungunya: young age and inefficient type-1 interferon signalling are risk factors for severe disease." *PLoS Pathog.* 2008 Feb 8; 4(2): e29.
(6) Ozden S et al. "Inhibition of Chikungunya virus infection in cultured human muscle cells by furin inhibitors: impairment of the maturation of the E2 surface glycoprotein." *J Biol Chem.* 2008 Aug 8; 283(32):21899-908.
(7) Bréhin AC et al. The large form of human 2',5'-Oligoadenylate Synthetase (OAS3) exerts antiviral activity against Chikungunya virus." *Virology.* 2009 Feb 5; 384(1): 216-22.

Yellow fever

Yellow fever is a zoonotic arbovirus carried by great apes in equatorial forests. It is transmitted to humans by mosquito bites. The formidable "urban form," which is increasingly present in African and South American metropolises, is a major cause of hemorrhagic fevers in those regions, despite the existence of an effective vaccine.

IN 2008

- ☐ completion of plans for a new yellow fever vaccine production unit at the Institut Pasteur in Dakar
- ☐ standardization of diagnostic tools for yellow fever at the African institutes in the RIIP
- ☐ assessment of the risk of a yellow fever epidemic in Europe

SURVEILLANCE AND PUBLIC HEALTH

The regional reference laboratory at the **Institut Pasteur in Dakar** confirmed a yellow fever epidemic in Côte d'Ivoire in the summer of 2008. Researchers in Dakar had already developed an integrated approach to yellow fever surveillance in 2003-2004[1].

The European Commission project **FP6-EDEN** is currently working to assess the risk of the emergence of arboviruses and hemorrhagic fevers in Europe using data on biotopes, disease history, bio-ecology of vectors and the impact on public health. The project involves 48 institutions including the **Institut Pasteur,** the **Cantacuzino Institute** (Romania), the **Institut Pasteur-Cenci Bolognetti Foundation**, and an Africa-based platform including the **Instituts Pasteur in Algeria** and **Dakar**.

Production of the yellow fever vaccine

In 2009, the yellow fever vaccine production unit at the **Institut Pasteur in Dakar** will be renovated and enlarged. Its production capacities will increase in order to meet the needs of health departments in African countries, at the request of the WHO.

DIAGNOSIS, TREATMENT, VACCINE

A project involving the **Instituts Pasteur in Dakar, Madagascar, Côte d'Ivoire** and **Bangui** and the **Pasteur Center in Cameroon**, as well as the BSL-4 laboratory in Lyon and Laboratory for Urgent Response to Biological Threats (CIBU) at the **Institut Pasteur**, will standardize and improve of diagnostic tools for hemorrhagic fevers. The project aims to strengthen detection capabilities related to the seven types of hemorrhagic fevers present in Africa: yellow fever, Lassa, dengue, Marburg, Ebola, Rift Valley fever and Crimean-Congo hemorrhagic fever. All of the reagents necessary for molecular and serological diagnosis have been made available to the participating laboratories and the first inter-laboratory quality control tests are currently underway.

The European Commission project "Viral Hemorrhagic Fever - Diagnostic" (**FP6-INCO**) unites the **Institut Pasteur in Dakar** and the **Institut Pasteur**. The project will enable development of rapid-results tests intended for use in front-line health posts. These tests will use dipsticks to diagnose viral hemorrhagic fevers. A real-time PCR mobile laboratory will be made available to the project.

The **Pasteur Center in Cameroon** and the **Instituts Pasteur in Dakar** and **French Guiana** are involved in a project aiming to establish the immune response to yellow fever and measles vaccines in young children.

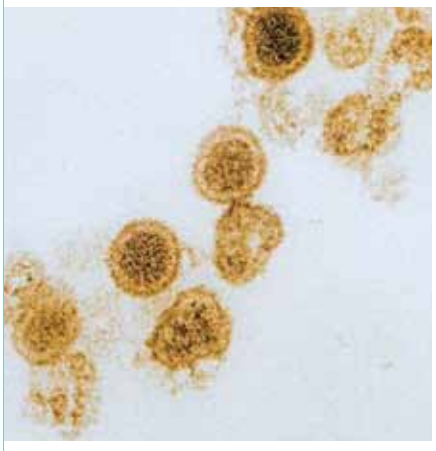
Finally, at the initiative of the WHO and its targeted program for tropical pathologies, the **Institut Pasteur in Cambodia** is proposing a project to evaluate diagnostic tests.

Diagnosis of hemorrhagic fevers

The "DEVA" research project, which includes researchers from the unit on Flavivirus-Host Molecular Interaction at the **Institut Pasteur**, is working to refine so-called "syndromic" DNA microarrays as applied to the diagnosis of the arboviruses responsible for hemorrhagic fevers, including yellow fever.

Rift Valley Fever

The **Institut Pasteur in Madagascar** and the National Reference Center for Arboviruses at the **Institut Pasteur** are collaborating on the PCS-MAE animal health surveillance program for Rift Valley Fever in the Indian Ocean region. The Arbovirus center is also partnering with the OIE and the ArboZoonet consortium for work on this disease, as well as with the InVS for surveillance on Mayotte Island. Finally, the Flavivirus-Host Molecular Interaction unit at the Institut Pasteur is developing new molecular diagnostic tools for this virus.



Virus of Rift Valley Fever. The virus is transmitted by a variety of mosquitoes. Colorized image.
© Topilko, A. / Institut Pasteur

(1) Faye O et al. "[Integrated approach to yellow fever surveillance: pilot study in Senegal in 2003-2004]." *Bull Soc Pathol Exot.* 2007 Aug; 100(3): 187-92.

Rabies

Rabies is a lethal viral infection of the nervous system that is endemic to numerous African and Asian countries. Each year, rabies causes between 40,000 and 70,000 human deaths despite the existence of an effective vaccine since its development by Louis Pasteur in 1885.

Rabies vaccination at the Institut Pasteur in Morrocco, circa 1950.
© *Institut Pasteur*

SURVEILLANCE AND PUBLIC HEALTH

The "STOPRAGE" project involving the **Instituts Pasteur in Dakar**, **Côte d'Ivoire** and **Bangui**, is working to implement human and animal rabies surveillance in West and central Africa to better assess the disease's incidence. This project includes four components: implementation of a local surveillance system, standardization of patient management, development of biological diagnostic techniques, and optimizing the use of epidemiological data.

These institutes are also part of the **AfroREB** network, along with the **Instituts Pasteur in Algeria, Morocco** and **Madagascar**; the **Pasteur Center in Cameroon**; and the WHO Collaborating Center on rabies at the **Institut Pasteur**. This AfroREB network of rabies experts performs information-sharing to improve rabies control programs in participating countries.

The **Institut Pasteur in Madagascar** performs active surveillance of bat colonies for the rabies virus.

In Asia, where rabies is also a threat, the **Institut Pasteur in Cambodia** conducted a study on all rabies cases in that country (1998-2007). Researchers emphasized the need to create a national rabies prevention program, improve surveillance activities, and expand access to post-exposure treatments.

In addition, the rabies treatment center at the **Institut Pasteur** evaluated France's national rabies surveillance program, which has identified 70 cases of the disease since 1970[1]. The Paris-based center dispenses some 4,000 post-exposure treatments per year. In 2008, it also diagnosed France's first indigenous case of rabies since 1924.

IN 2008

- ☐ development of diagnostic techniques using skin biopsies in an intra-RIIP collaboration
- ☐ first description of the genetic diversity of lyssaviruses at Institut Pasteur
- ☐ investigation of the potential of adenoviruses for the development of a canine rabies vaccine at the Institut Pasteur

Finally, the **Institut Pasteur in French Guiana** handles preventive measures for all exposed persons and conducts regular surveillance activities in the context of the V.I.R.U.S.E.S. program.

EPIDEMIOLOGY

RIIP institutes administered 500,000 doses of rabies vaccine worldwide in 2008.

The European Union's **"RABMEDCONTROL"** project includes nine institutes in the greater Mediterranean area, including the **Instituts Pasteur in Tunis** and **Algeria** and the **Institut Pasteur.** Its goal is to collect epidemiological and virological data on human and animal rabies in North Africa. This research has provided a better understanding of the ecological aspects of dog and bat populations, as well as of human behaviors that influence the transmission of rabies. This multidisciplinary data will provide the basis for new recommendations on rabies control in North Africa.

The **Institut Pasteur in Iran** conducted an epidemiological study on the incidence of rabies in Iran. Researchers clarified the role of wolves as the main reservoir for rabies in Iran[2].

The National Reference Center for rabies at the **Institut Pasteur**, which is also a WHO Collaborating Center, analyzed changes in the incidence of rabies in bat colonies in Europe over a 12-year period. This work demonstrates that the proportion of immune and infected bats varies over time[3].

(1) Rotivel Y. "Epidemiology and prophylaxis of rabies in humans in France: evaluation and perspectives of a twenty-five year surveillance programme." *Dev Biol (Basel).* 2008; 131:403-10.
(2) Janani AR et al. "Epidemiology and control of rabies in Iran." *Dev Biol (Basel).* 2008; 131:207-11.
(3) Amengual B et al. "Temporal dynamics of European bat Lyssavirus type 1 and survival of Myotis myotis bats in natural colonies." *PLoS ONE.* 2007 Jun 27; 2(6): e566.

GENETIC AND MOLECULAR STUDIES

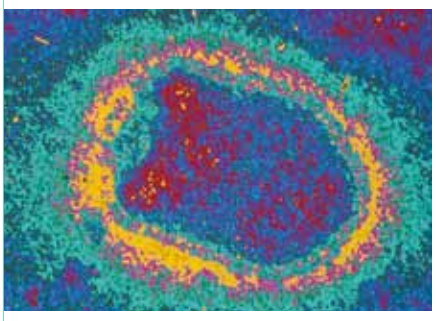
The National Reference Center for rabies at the **Institut Pasteur** published the first genomic and evolutionary analysis of all known lyssavirus genotypes[4]. In another study published with the **Instituts Pasteur in Dakar, Bangui** and **Côte d'Ivoire**, the Reference Center's researchers analyzed the phylogeography of the rabies virus in dogs[5].Other results from the same project concern the genetic origins of rabies strains circulating in West and central Africa; these results will be published in 2009[6].

MOTHER-TO-CHILD TRANSMISSION

The Virology unit at the **Institut Pasteur in Madagascar** reported the case of a baby born prematurely but healthy to a mother infected with the rabies virus. This work should lead to new clinical guidelines for managing rabies-infected pregnant women[7].

IMMUNOLOGY

The Neuroimmunology unit at the **Institut Pasteur** established the exacerbating role of the natural immune inhibitor B7-H1 in rabies-related encephalitis in mice[8].



Rabies virus.
© *Dauguet, C. ; Atanasiu, P. ; Service photo / Institut Pasteur*

Some species of bats can be vectors for rabies, mostly in North and South America.
© *Dodin, A. / Institut Pasteur*

DIAGNOSIS, TREATMENT, VACCINE

Researchers at the National Reference Center for rabies at the **Institut Pasteur** worked with the **Instituts Pasteur in Cambodia, Madagascar** and **Dakar** on a new diagnostic method using skin biopsies. This technique has proven to be more sensitive than the biological diagnosis methods (saliva, urine) that are currently in use[9].

Other diagnostic techniques using non-specific amplification of virological RNA and DNA microarrays have been developed by the **Institut Pasteur** and the **Institut Pasteur in Dakar**[10].

The **Instituts Pasteur in Tunis** and **Algeria**, along with the three **Instituts Pasteur in Vietnam**, are involved in the development of a rabies vaccine for humans and rabies serum. In addition, researchers at the **Institut Pasteur in Tunis** published an important article on the canine vaccine[11], in which they reported the development of a new technique for culturing the rabies virus. This technique does not use any components of human or animal origin[12]. At the **Scientific Institute of Public Health** in Belgium, researchers are developing a new type of antiviral for prophylaxis and treatment of rabies.

Finally, researchers from the **Institut Pasteur** helped run a randomized controlled trial to test the human intradermal vaccine. This trial involved four sites, and the vaccine proved to be less costly and equally as effective as competing methods[13]. Another study identified the potential role of adenovirus vectors in the development of an oral rabies vaccine for dogs[14].

Vaccination against rabies, Institut Pasteur circa 1910.
© *Institut Pasteur*

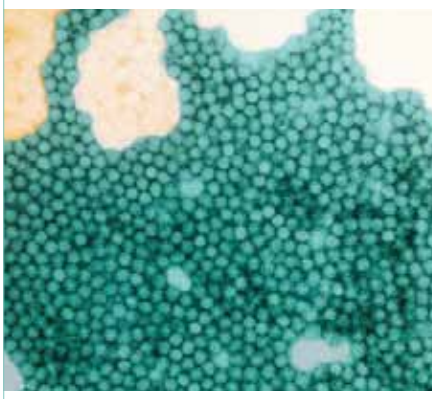
(4) Delmas O et al. "Genomic diversity and evolution of the lyssaviruses." *PLoS ONE.* 2008 Apr 30; 3(4): e2057.
(5) Bourhy H et al. "The origin and phylogeography of dog rabies virus." *J Gen Virol.* 2005 Aug; 79(16): 10487-97.
(6) Talbi C et al. "Evolutionary history and dynamics of dog rabies virus in western and central Africa." *J Gen Virol Direct.* 2009 Jan 9.
(7) Iehlé C et al. "Delivery and follow-up of a healthy newborn from a mother with clinical rabies." *J Clin Virol.* 2008 May; 42(1): 82-5.
(8) Lafon M et al. "Detrimental contribution of the immuno-inhibitor B7-H1 to rabies virus encephalitis." *J Immunol.* 2008 Jun 1; 180(11): 7506-15.
(9) Dacheux L et al. "A reliable diagnosis of human rabies based on analysis of skin biopsy specimens." *Clin Infect Dis.* 2008 Dec 1; 47(11): 1410-7.
(10) Berthet N et al. "Phi29 polymerase based random amplification of viral RNA as an alternative to random RT-PCR." *BMC Mol Biol.* 2008 Sept 4; 9: 77.
(11) Bahloul C et al. "Field trials of a very potent rabies DNA vaccine which induced long lasting virus neutralizing antibodies and protection in dogs in experimental conditions." *Vaccine.* 2006 Feb 20; 24(8): 1063-72.
(12) Rourou S et al. "A microcarrier cell culture process for propagating rabies virus in Vero cells grown in a stirred bioreactor under fully animal component free conditions." *Vaccine.* 2007 May 10; 25(19) 3879-89.
(13) Warrell M et al. A simplified 4-site economical intradermal post-exposure rabies vaccine regimen : a randomized controlled comparison with standard methods. *PLoS Negl Trop Dis.* 2008 Apr 23; 2(4): e224.
(14) Tordo N et al. "Canine adenovirus based rabies vaccines." *Dev Biol (Basel).* 2008; 131: 467-76.

Poliomyelitis

The goal of eradicating poliomyelitis worldwide is challenged by the emergence of new recombinant viruses (vaccination-related polioviruses and circulating enteroviruses).

IN 2008

- ☐ emphasis on the co-circulation and co-evolution of polioviruses derived from vaccines in Madagascar
- ☐ identification of the increased pathogenicity of recombinant poliovirus strains with other enterovirus strains at the Institut Pasteur
- ☐ genotyping of various poliovirus strains in Tunisia



Poliovirus, agent of poliomyelitis, for which man is the only natural host. Colorized image.
© *Dauguet, C. / Institut Pasteur*

SURVEILLANCE AND PUBLIC HEALTH

Recent advances in the fight against polio are threatened by epidemics of a new type. These are caused by recombinant viruses made up of vaccine-derived poliovirus strains and other unidentified enteroviruses. For this reason, the **Instituts Pasteur in Saint Petersburg** and **Dakar,** the **Cantacuzino Institute** (Romania), and the **Institut Pasteur** have created the project "Circulation of polioviruses and nonpolio enteroviruses in the environment" This project is assessing the risk of re-emergence of recombinant strains in waste water.

Other enteroviruses

A project including the **Institut Pasteur in Madagascar**, the **Pasteur Center in Cameroon** and the **Institut Pasteur's** Molecular Prevention and Therapy of Human Diseases Unit, is seeking to identify enterovirus strains circulating in non-human primates in Africa.

EPIDEMIOLOGY

The **Institut Pasteur in Madagascar,** a WHO national reference laboratory for poliomyelitis, is collaborating with the **Institut Pasteur** unit on Enteric Virus Biology to research the emergence of new poliovirus strains. They have identified multiple vaccine-derived polioviruses and other circulating enteroviruses in the southern province of Madagascar [1]. Researchers then described the re-emergence of recombinant poliovirus strains through epidemiological and virological approaches. The results suggest co-circulation and co-evolution of these strains with group C enteroviruses [2].

The WHO regional reference laboratory at the **Institut Pasteur in Bangui**, in collaboration with researchers from the I**nstitut Pasteur,** is working on the RFLP technique, which enables comparison of the RNA from various strains of circulating poliovirus [3].

Polio vaccination campaign in Vietnam.
© *IP Vietnam / Institut Pasteur*

The clinical virology laboratory at the **Institut Pasteur in Tunis,** a WHO regional reference centre for poliomyelitis, completed genotyping of wild and vaccine-derived poliovirus strains [4]. Finally, the **Institut Pasteur in Greece** reported a rare type of recombination in an oral vaccine-derived polioviruses [5].

BASIC RESEARCH

Researchers from the **Institut Pasteur** proved the link between the pathogenicity of recombinant polioviruses and type C enteroviruses [6].

(1) Rakoto-Andrianarivelo M et al. "Co-circulation and evolution of polioviruses and species C enteroviruses in a district of Madagascar." *PLoS Pathog.* 2007 Dec; 3(12): e191.
(2) Rakoto-Andrianarivelo M et al. "Reemergence of recombinant vaccine-derived poliovirus outbreak in Madagascar." *J Infect Dis.* 2008 May 15; 197(10): 1427-35.
(3) Gouandjika-Vasilache I et al. "Molecular epidemiology of wild poliovirus type 1 circulation in West and Central Africa, from 1997 to 1999, using genotyping with a restriction fragment length polymorphism assay." *Arch Virol.* 2008;153(3):409-16.
(4) Haddad-Boubaker S et al. "Genetic features of polioviruses isolated in Tunisia, 1991-2006." *J Clin Virol.* 2008 Feb;41(2):81-6. Epub 2007 Nov 26.
(5) Karakasiliotis I et al. "Evolution of a rare vaccine-derived multirecombinant poliovirus." *J Gen Virol.* 2005 Nov;86(Pt 11):3137-42.
(6) Riquet FB et al. "Impact of exogenous sequences on the characteristics of an epidemic type 2 recombinant vaccine-derived poliovirus." *J Virol.* 2008 Sept; 82(17): 8927-32

Encephalitis

The term "viral encephalitis" applies to diseases of the central nervous system with causal agents that can belong to various virus families, including Paramyxovirus, Flavivirus and Enterovirus.

IN 2008

- ☐ launch of a Vietnamese project on the putative Ac Mong ("nightmare") virus, a new cause of pediatric encephalitis
- ☐ description of the activity of immunologic cells during encephalitis caused by West Nile virus by the Institut Pasteur

Institut Pasteur in Cambodia.

SURVEILLANCE AND PUBLIC HEALTH

The **Institut Pasteur in Cambodia** began surveillance of patients with encephalitis in order to detect the emergence of the Nipah virus. In addition to human surveillance, the researchers analyzed virus strains isolated from bats in collaboration with researchers at the **Institut Pasteur** [1].

In Europe, the National Reference Center for Arboviruses at the **Institut Pasteur** is a primary player in surveillance of the viruses responsible for encephalitis, such as West Nile virus.

EPIDEMIOLOGY

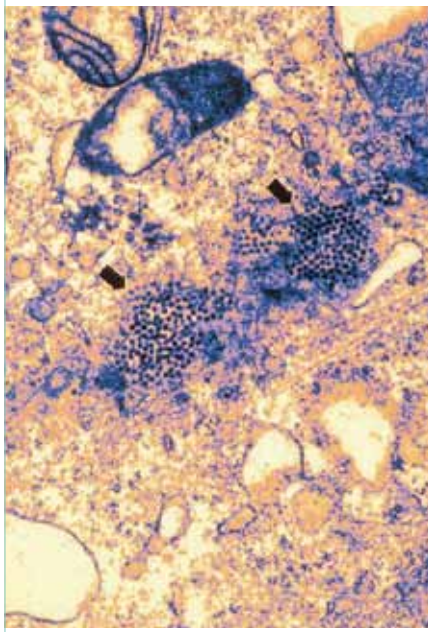
The **Institut Pasteur in Ho Chi Minh City** identified the role of enterovirus infections in children presenting symptoms of hand-foot-mouth disease associated with encephalitis. Approximately 42% of the 764 children were infected with enterovirus 71 and 52% with Coxsackievirus A16 [2].

GENETIC AND MOLECULAR STUDIES

The **NIHE** in Hanoi is directing the **BASE** project (Bac giang Acute Syndrome of Encephalitis) in collaboration with the Laboratory for Urgent Response to Biological Threats (CIBU), among other units, at the **Institut Pasteur**. This project is seeking to characterize the putative Ac Mong ("nightmare") virus, an emerging virus responsible for encephalitis in Vietnamese children.

Researchers from the **Instituts Pasteur in Shanghai** and **Cambodia** are studying the molecular aspects of the pathogenesis of Japanese encephalitis.

At the **Institut Pasteur**, researchers are participating in a project on the genetic components of sensitivity to West Nile virus.



West Nile virus. A cell performing vival production (see arrows).
© *Le Guenno, B. / Institut Pasteur*

DIAGNOSIS, TREATMENT, VACCINES

The National Reference Center for Arboviruses at the **Institut Pasteur** is collaborating with the **Institut Pasteur in Shanghai** to validate new diagnostic tools for Japanese encephalitis.

Researchers from the **Institut Pasteur's** Flavivirus-Host Molecular Interactions unit developed new diagnostic tools for infection by the West Nile virus, which are currently undergoing final testing at the European level.

Finally, many units at the **Institut Pasteur** are jointly pursuing the development of a vaccine for West Nile virus, based on the use of a lentiviral vector [3].

IMMUNOLOGY

Two units at the **Institut Pasteur** published an article on the recruitment by West Nile virus of peripheral immune cells in a murine model of encephalitis caused by West Nile Virus [4].

(1) Reynes JM et al. "Nipah virus in Lyle's flying foxes." *Emerg Infect Dis.* 2005 Jul; 11(7): 1042-7.
(2) Tu PV et al. "Epidemiologic and virologic investigaton of hand, foot, and mouth disease, southern Vietnam, 2005." *Emerg Infect Dis.* 2007 Nov; 13(11): 1733-41.
(3) Coutant F et al. "Protective antiviral immunity conferred by a nonintegrative lentiviral vector-based vaccine." *PLoS ONE.* 2008; 3(12): e3973.
(4) Bréhin et al. "Dynamics of immune cell recruitment during West Nile encephalitis and identification of a new CD19+B220-BST-2+ leukocyte population." *J Immunol.* 2008 May 15; 180(10): 6760-7.

Papillomavirus

Ten to thirty percent of the human population is infected by papillomaviruses. A vaccine exists against certain strains of the virus, which are sometimes oncogenic and can cause cervical cancer.

EPIDEMIOLOGY

The **Institut Pasteur in Iran** conducted a study suggesting that papillomavirus infection plays a role in tumor development in Iranian patients who have cancers of the esophagus [1].

Researchers at **Fiocruz** in Brazil identified various factors associated with papillomavirus infection in HIV-positive women, such as young age and advanced immunodepression [2].

GENETIC AND MOLECULAR STUDIES

The **Institut Pasteur**'s Molecular Retrovirology Unit looked at mutations in the APOBEC3 genes, which seem to influence the development of tumors [3]. The Genetic Expression and Diseases Unit described a new E6/P63 route which modulates the transcriptome of cervical tumor cells [4].

The Molecular Virology Unit of the **Scientific Institute of Public Health** in Brussels evaluated PCR genotyping strategies for papillomavirus, using cervical tissue samples [5]. Researchers also organized a RIIP/INTCR worshop on the detection of human papillomavirus [6].

DIAGNOSIS, TREATMENT, VACCINE

A study performed by researchers at the **Institut Pasteur** suggests that the benefits of papillomavirus vaccination might be maximized through use of the Gp96 protein, which stimulates E7 immune response [7].

Another oncogenic virus: HTLV-1

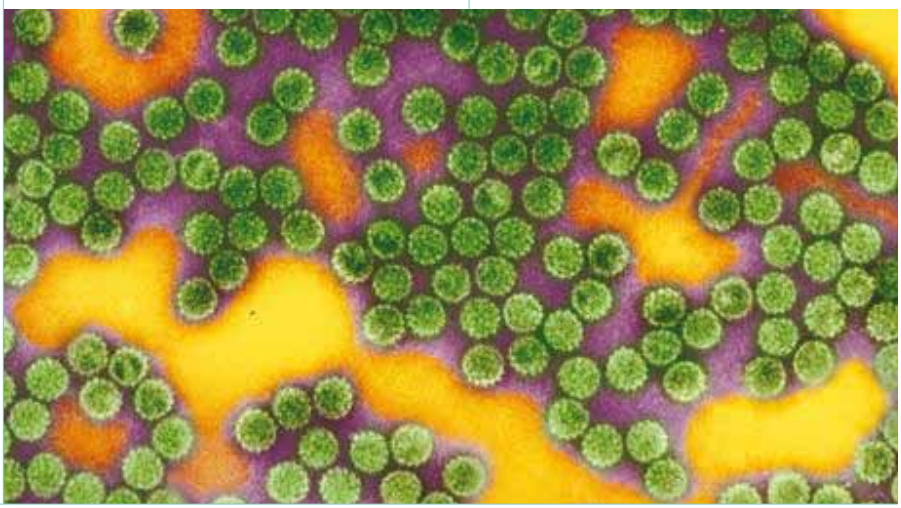
The Oncogenic Virus Epidemiology and Pathology Unit at the **Institut Pasteur** is currently working on HTLV-1 epidemiology in French Guiana, Central Africa and Melanesia. In 2008, this unit showed that HTLV-1 infection can damage the blood-brain barrier [8]. In addition, the **Institut Pasteur in New Caledonia** published a study on the incidence and molecular origins of HTLV-1 in the Vanuatau archipelago in the south-western Pacific Ocean, where the disease is endemic [9]. The **Institut Pasteur in French Guiana** also developed an animal model for studying immunologic changes and the expression of cytokine genes in response to HTLV-1 infection [10].

IN 2008

- ☐ study on the role of papillomavirus in cancers of the esophagus by the Institut Pasteur in Iran
- ☐ identification of a protein that may improve vaccine effectiveness at the Institut Pasteur
- ☐ identification of human genetic changes that might promote tumor development at the Institut Pasteur

In January 2009, the **Institut Pasteur** announced the creation of a National Reference Center for Papillomavirus, which will provide expert advice, surveillance, governmental notification, training, and technical assistance to laboratories.

Papillomavirus. Causes a proliferationof the epithelium leading to growths that are usually benign and sometimes cancerous. Colorized image.



(1) Far AE et al. "Frequency of human papillomavirus infection oesophageal squamous cell carcinoma in Iranian patients." *Scand J Infect Dis.* 2007; 39(1): 58-62.
(2) Grinsztein B et al. "Factors associated with increased prevalence of human papillomavirus infection in a cohort of HIV-infected Brazilian women." *Int J Infect Dis.* 2009 Jan; 13(1): 72-80.
(3) Vartanian JP et al. "Evidence for editing of human papillomavirus DNA by APOBEC3 in benign and precancerous lesions." *Science.* 2008 Apr 11; 320(5873): 230-3.
(4) Teissier S et al. "A new E6/P63 pathway, together with a strong E7/E2F mitotic pathway, modulates the transcriptome in cervical cancer cells." *J Virol.* 2007 Sep; 81(17): 9368-76.
(5) Fontaine V et al. "Evaluation of combined general primer-mediated PCR sequencing and type-specific PCR strategies for determination of human papillomavirus genotypes in cervical cell specimens." *J Clin Microbiol.* 2007 Mar; 45(3): 928-34.
(6) Weyn C et al. "Detection of human Papillomavirus types 45 and 51 by type-specific polymerase chain reaction." 2007 Dec; 146(1-2): 405-8.
(7) Bolhassani A et al. "Enhanced immunogenicity of HPV16E7 accompanied by Gp96 as an adjuvant in two vaccination strategies." *Vaccine.* 2008 Jun 19; 26(26): 3362-70.
(8) Afonso PV et al. "Alteration of blood-brain barrier integrity by retroviral infection." *PLoS Pathog.* 2008 Nov 4; 4(11): e10000205.
(9) Cassar O et al. "Human T lymphotropic virus type 1 subtype C Melanesian genetic variants of the Vanuatu Archipelago and Solomon Islands share a common ancestor." *J Infect Dis.* 2007 Aug 15; 196(4): 510-21.
(10) Heraud JM et al. "Immunological changes and cytokine gene expression during primary infection with juman T-cell leukaemia virus type 1 in squirrel monkeys (Saimiri sciureus)." *Virology.* 2007 May 10; 361(2): 402-11.

BACTERIAL DISEASES

To learn more about research on diseases at the Institut Pasteur – too extensive to be detailed here – visit:
www.pasteur.fr

Tuberculosis

Tuberculosis, an airborne bacterial infection, is responsible for 1.6 million deaths per year. Though approximately one-third of the current human population is infected with the bacillus, the most worrying aspects of the disease involve high rates of undiagnosed patients, frequent co-infection with HIV, and circulation of multidrug resistant strains.

IN 2008

- ☐ identification of predictors of pulmonary tuberculosis in HIV-infected Asian patients by the Instituts Pasteur in Cambodia and Vietnam
- ☐ research on the role of Beijing strains of tuberculosis in Russia's worrying epidemiological situation
- ☐ new findings on genetic interaction between *Mycobacterium tuberculosis* and its human host cells published by the Institut Pasteur

SURVEILLANCE AND PUBLIC HEALTH

The **Instituts Pasteur in Bangui**, **Côte d'Ivoire**, **Dakar**, **Madagascar**, **Guadeloupe**, **Cambodia**, **Ho Chi Minh City**, **Saint Petersburg**, **Algeria**, **Morocco**, and **Tunis**, as well as the **Pasteur Center in Cameroon** and the **Scientific Institute of Public Health** in Brussels all participate in national programs for the fight against tuberculosis in their respective countries, including surveillance and diagnostic activities.

In May 2008, the **Institut Pasteur** organized a training workshop on genetic and molecular aspects of tuberculosis with the CDC in Shanghai. The course was attended by scientists from the Instituts Pasteur in Korea, Vietnam, Cambodia, Morocco, and Dakar, as well as the Cantacuzino Institute (Romania) and the Stephen Angeloff Institute (Bulgaria). Website: www.moleculartb.org

EPIDEMIOLOGY

The **Stephan Angeloff Institute** compared strains of *M. tuberculosis* isolated in Bulgaria with the database of strains at the **Institut Pasteur in Guadeloupe** and found both Balkan-specific and world-distributed spoligotypes. The Beijing genotype was not found despite close contacts with Russia [1].

Researchers at the **Institut Pasteur in Tunis** published research showing a highly homogenous population of *M. tuberculosis*, likely due to mass BCG vaccination and high endogamy rates [2].

The **Institut Pasteur in Saint Petersburg** examined the molecular diversity of *M. tuberculosis* in the Kaliningrad region of Russia, highlighting the nefarious role of the Beijing genotype in the regional epidemiological situation [3]. An in-depth study of the Beijing strains suggests that their evolution closely follows patterns of human genetic diversity [4].

At the **Institut Pasteur in Guadeloupe**, researchers analyzed an international database containing some 71,000 tuberculosis DNA fingerprints from 160 countries. The results suggest minute genetic variations of the *M. tuberculosis* complex, which could mirror human demographic history [5]. Another study on the epidemiological profile of tuberculosis in Guadeloupe showed it to be similar to that of industrialized countries [6].

GENETIC AND MOLECULAR STUDIES

The **Institut Pasteur** investigated gene expression changes in *M. tuberculosis* and in its

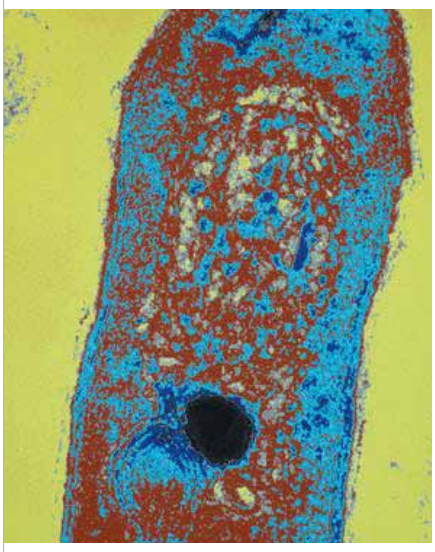
(1) Valcheva V et al. "Molecular characterization of Mycobacterium tuberculosis isolates from different regions of Bulgaria." *J Clin Microbiol.* 2008 Mar; 46(3): 1014-8.
(2) Namouchi A et al. "Genetic profiling of Mycobacterium tuberculosis in Tunisia: predominance and evidence for the establishment of a few genotypes." *J Med Microbiol.* 2008 Jul; 57(Pt 7): 864-72.
(3) Mokrousov I et al. "At Baltic crossroads: a molecular snapshot of Mycobacterium tuberculosis population diversity in Kaliningrad, Russia." *FEMS Immunol Med Microbiol.* 2008 Sep 17. [Epub ahead of print.]
(4) Mokrousov I. "Genetic geography of Mycobacterium tuberculosis Beijing genotype: a multifacet mirror of human history?" *Infect Genet Evol.* 2008 Dec; 8(6): 777-85.
(5) Brudey K et al. "Mycobacterium tuberculosis complex genetic diversity: mining the fourth international spoligotyping database (SpolDB4) for classification, population genetics and epidemiology." *BMC Microbiol.* 2006 Mar 6, 6:23.
(6) Brudey K et al. "[Molecular epidemiology of tuberculosis in Guadeloupe from 1994 to 2000]." *Pathol Biol (Paris).* 2006 Feb; 54(1): 14-21.

human host cells (macrophages and dendritic cells), demonstrating an "extraordinary plasticity" of host and pathogen responses to infection [7]. The same team analyzed the DNA repair, recombination and replication (3R) genes of *M. tuberculosis* using bioinformatics, yielding unexpectedly high levels of polymorphisms driven by this family [8].

The **Institut Pasteur in Saint Petersburg** published an article identifying one allele as a possible risk factor for developing tuberculosis in the Slavic population of Saint Petersburg, while dismissing another polymorphism as a factor of susceptibility to the disease [9].

Researchers from the **Institut Pasteur in Lille** reported on a three-year population-based study of *M. tuberculosis* strains, reinforcing the use of the MIRU-VNTR technique in epidemiological and phylogenetic screening [10].

The **Institut Pasteur in Tunis** developed a microarray targeting nearly all of the PE/PPE multigene families of *M. tuberculosis*. Researchers used this microarray to detect significant levels of homologous recombination, which may have important implications regarding pathogenicity [11].
Finally, the **Institut Pasteur** and **Institut Pasteur in Korea** collaborate on the "TB VIR" program, financed under the European FP7, which studies the genetic diversity of *M. tuberculosis* strains of the W-Beijing family, its differential virulence, and host immune responses.



Mycobacterium tuberculosis.
© Ryter A, Service photo/Institut Pasteur

DIAGNOSIS, THERAPY, VACCINE

The **Institut Pasteur in Madagascar**, home to a National Reference Center for tuberculosis, evaluated a rapid culture method for isolating *M. tuberculosis*, and determined that the process was faster but not more accurate with the liquid Bio FM medium than with the Löwenstein-Jengen medium [12].

In Yaoundé, the **Pasteur Center in Cameroun** determined that the bleach sputum concentration technique can incrementally improve diagnosis rates for HIV-positive patients of tuberculosis [13].

At the **Institut Pasteur in Lille**, researchers working on tuberculosis vaccines studied latent infections, and suggested that bacteria may reside within non-macrophage cell types throughout the infected body [14].

The **Institut Pasteur** determined that natural regulatory T cells (Treg) have a significant negative effect on the efficacy of the BCG vaccine, though this cell population is not the major cause of the vaccine's limited efficacy [15]. In another study, researchers demonstrated that oral prime vaccination with BCG plus intranasal boost with a candidate vaccine provides protection equivalent to subcutaneous prime-boost immunization [16].

At the **Scientific Institute of Public Health** in Brussels, researchers demonstrated that BCG vaccine efficacy in mice can be improved by plasmid DNA vaccination [17]. Also, biochemical studies revealed a key enzyme for vitamin C biosynthesis in *M. tuberculosis* and its relation to a pathway targeted by ethambutol, an antituberculosis drug [18].

CO-INFECTION

Researchers studying HIV/tuberculosis co-infection have launched **CAMELIA** (CAMbodia, Early vs. Late Introduction of Antiretroviral therapy), a project intended to clarify whether treatments for the two diseases should be administered simultaneously or one after the other. The two partners in **CAMELIA**, the **Institut Pasteur** and the **Institut Pasteur in Cambodia**, also performed a study on HIV-positive Asian patients to identify predictors of *Pneumocystis jiroveci pneumonia* and pulmonary tuberculosis [19].

(7) Tailleux L et al. "Probing host pathogen cross-talk by transcriptional profiling of both Mycobacterium tuberculosis and infected human dendritic cells and macrophages." *PLoS ONE*. 2008 Jan 2; 3(1): e1403.
(8) Dos Vultos T et al. "Evolution and diversity of clonal bacteria: the paradigm of Mycobacterium tuberculosis." *PLoS ONE*. 2008 Feb 6; 3(2): e1538.
(9) Mokrousov I et al. "Mycobacterium tuberculosis co-existence with humans: making an imprint on the macrophage P2X(7) receptor gene?" *J Med Micrbiol*. 2008 May; 57 (Pt 5): 581-4.
(10) Allix-Béguec C et al. "Three-year population-based evaluation of standardized mycobacterial interspersed repetitive-unit-variable-number tandem-repeat typing of Mycobacterium tuberculosis." *J Clin Microbiol*. 2008 Apr; 46(4): 1398-406.
(11) Karboul A et al. "Frequent homologous recombination events in Mycobacterium tuberculosis PE/PPE multigene families: potential role in antigenic variability." *J Bacteriol*. 2008 Dec; 190(23): 7838-46.
(12) Ramarokoto H et al. "Evaluation of a rapid culture method on liquid Bio FM (BIO-RAD) medium for the isolation of mycobacteria." *Int J Tuberc Lung Dis*. 2007 Aug; 11(8): 898-903.
(13) Eyangoh SI et al. "HIV-related incremental yield of bleach sputum concentration and fluorescence technique for the microscopic detection of tuberculosis." *Eur J Clin Microbiol Infect Dis*. 2008 Sep; 28(9): 849-55.
(14) Locht C et al. "How a different look at latency can help develop novel diagnostics and vaccines against tuberculosis." *Expert Opin Biol Ther*. 2007 Nov; 7(11): 1655-77.
(15) Jaron B et al. "Effect of attenuation of Treg during BCG immunization on anti-mycobacterial Th1 responses and protection against Mycobacterium tuberculosis." *PLoS ONE*. 2008 Jul 30; 3(7): e2833.
(16) Badell E et al. "Protection against tuberculosis induced by oral prime with Mycobacterium bovis BCG and intranasal subunit boost based on the vaccine candidate Ag85B-ESAT-6 does not correlate with circulating IFN-gamma producing T-cells." *Vaccine*. 2009 Jan 1; 27(1): 28-37.
(17) Roupie V et al. "Immunogenicity of eight dormancy (DosR) regulon encoded proteins of Mycobacterium tuberculosis in DNA vaccinated and tuberculosis-infected mice." *Infect Immun*. 2007 Feb. 75(2): 941-949.
(18) Wolucka BA. "Biosynthesis of D-arabinose in mycobacteria: a novel bacterial pathway with implications for antimycobacterial therapy." *FEBS J*. 2008 Jun. 275(11): 2691-2711.
(19) Le Minor O et al. "Predictors of pneumocystosis or tuberculosis in HIV-infected Asian patients with AFB smear-negative sputum pneumonia." *J Acquir Immune Defic Syndr*. 2008 Aug 15; 48(5): 620-7.

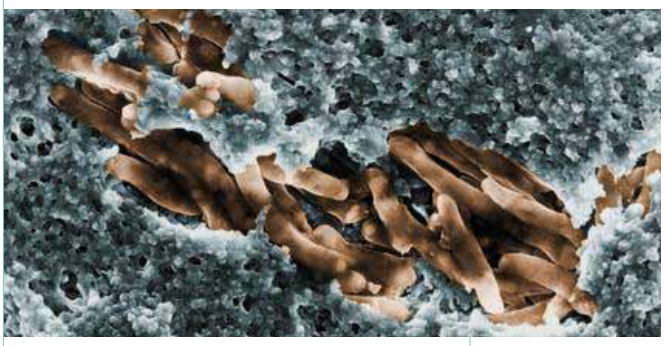
Buruli ulcer

Buruli ulcer is a condition that occurs predominantly in tropical regions, mostly in central and West Africa. The disease brings about massive skin destruction and is caused by Mycobacterium ulcerans, *a relative of the leprosy pathogen. Currently, the only available treatment is to excise the ulcer, though RIIP member institutes are seeking new tools to fight the disease via extensive field and laboratory research.*

IN 2008

☐ identification of various risk factors and protective behaviors for Buruli ulcer in Cameroon

☐ publication of a proteome analysis of Mycobacterium ulcerans by the Institut Pasteur



Mycobacterium ulcerans, causal agent of Buruli ulcer, as seen through an electronic microscope. Buruli ulcer is the third most-common mycobacterial infection worlwide. Colorized image. © *Marsollier, L. / Institut Pasteur*

EPIDEMIOLOGY

The **Pasteur Center in Cameroon** performed a case-control study on *M. ulcerans* infections and identified risk factors (low education levels, swamp wading, wearing shorts while farming) as well as protective factors (using bed nets, washing clothes, using leaves as traditional treatment when injured) [1].

Researchers at the **Pasteur Center in Cameroon** also collaborate with the **Institut Pasteur in Côte d'Ivoire** in a project comparing epidemiological, environmental, and genetic parameters of Buruli ulcer, for which results are forthcoming.

The Institut Pasteur has sequenced the genome of an epidemic strain of *Mycobacterium ulcerans* and made it available to researchers at the following website: http://genolist.pasteur.fr/BuruList/

GENETIC AND MOLECULAR RESEARCH

The **Institut Pasteur** reported the complete genome sequence of *M. ulcerans* and postulated that it evolved via lateral gene transfer from the *M. marinum* species to become a niche-adapted specialist[2].

DIAGNOSIS, THERAPY, VACCINE

Researchers at the **Institut Pasteur in Côte d'Ivoire** evaluated the use of PCR to diagnose infection by *M. ulcerans* in specimens of exudates and biopsies, and found that the technique can be used to confirm a routine specific diagnosis and to perform early screening[3].

At the **Institut Pasteur**, it was shown that subcutaneous vaccination with BCG provided a substantial degree of protection against *M. ulcerans* in mice[4].

IMMUNOLOGY

Researchers at the **Institut Pasteur** investigated the effect of a toxin produced by *M. ulcerans*, mycolactone, on dendritic cells, and found that it may limit the initiation of primary immune response and the recruitment of inflammatory cells to the infection site[5].

On the other hand, researchers at the **Scientific Institute of Public Health** in Brussels demonstrated that a booster immunization with BCG did not increase the efficacy of the vaccine against experimental *M. ulcerans* infection in mice[6]. They also showed that the efficacy of a DNA vaccine encoding mycolyl-transferase Ag85A from *M. ulcerans* could be increased by homologous protein boosting[7].

BASIC RESEARCH

At the **Institut Pasteur**, researchers at the Proteomics Platform recently published a comprehensive proteome analysis of different subcellular fractions and culture supernatant of the pathogen[8]. Another group of researchers, working closely with a team at the **Institut Pasteur in Korea**, studied the role of biofilms in the pathogenesis of *M. ulcerans*, finding that it confers increased resistance to antimicrobial agents[9]. The same groups also demonstrated a protective effect of exposure to bites from predatory aquatic insects[10] after tracking the pathogen's path through the vector's salivary gland.[11]

(1) Pouillot R et al. "Risk factors Buruli ulcer: a case control study in Cameroon." *PLoS Negl Trop Dis.* 2007 Dec 19; 1(3): e101.
(2) Stinear TP et al. "Reductive evolution and niche adaptation inferred from the genome of M. ulcerans, the causative agent of Buruli ulcer." *Genome Res.* 2007 Feb; 17(2): 192-200.
(3) Ekaza et al. "[Contribution of gene amplification in M. ulcerans detection in exudates and cutaneous biopsies in Côte d'Ivoire.]" *Bull Soc Pathol Exot.* 2004 May; 97 (2): 95-6.
(4) Coutanceau E et al. "Immunogenicity of M. ulcerans Hsp65 and protective efficacy of a M. leprae Hsp65-based DNA vaccine against Buruli ulcer." *Microbes Infect.* 2006 Jul; 8(8): 2075-81.
(5) Coutanceau E et al. "Selective suppression of dendritic cell functions by M. ulcerans toxin mycolactone." *J Exp Med.* 2007 Jun 11; 204(6): 1395-403.
(6) Thange et al. "A booster vaccinationwith M. bovis BCG does not increase the protective effect of the vaccine against experimental Mycobacterium ulcerans infection in mice." *Infect Immun.* 2007 May; 75(5): 2642-4.
(7) Thange et al. "Improved protective efficacy of a species-specific DNA vaccine encoding mycolyl-transferase Ag85A from M. ulceran by homologous protein boosting." *Plos Negl Trop Dis.* 2008 Mars 19; 2(3): e99.
(8) Tafelmeyer P et al. "Comprehensive proteome analysis of M. ulcerans and quantitative comparison of mycolactone biosynthesis." *Proteomics.* 2008 Aug; 8(15): 3124-38.
(9) Marsollier L et al. "Impact of M. ulcerans biofilm on transmissibility to ecological niches and Buruli ulcer pathogenisis." *PLoS Pathog.* 2007 May 4; 3(5): e62.
(10) Marsollier L et al. "Protection against M. ulcerans lesion development by exposure to aquatic insect saliva." *PLoS Med.* 2007 Feb; 4(2): e63.
(11) Marsollier L et al. "Early trafficking events of M. ulcerans within Naucoris cimicoides." *Cell Microbiol.* 2007 Feb; 9(2): 347-55.

Cholera

Cholera is a highly infectious bacterium transmitted through contaminated food and drinking water. The disease can kill within hours of infection and thrives in unhygienic or unstable conditions, such as conflicts and natural disasters.

Students at the NIHE in Hanoi.

SURVEILLANCE AND PUBLIC HEALTH

The **Institut Pasteur in Algeria** performs surveillance and epidemiological control in case of cholera outbreaks. The **Institut Pasteur in Nha Trang** also performs disease control for cholera. The **CERMES** in Niger acts as a diagnostic and typing laboratory for the Ministry of Public Health to confirm possible cholera outbreaks.

Following an outbreak of cholera in Vietnam in 2008, the National Reference Center for vibrions and cholera at the Institut Pasteur responded in a collaborative effort with the **NIHE in Hanoi**.

Researchers at the **Cantacuzino Institute** in Romania created a database of ribotypes and pulse field gel electrophoresis profiles of *V. cholerae* 01 trains circulating in Romania and Moldova.

EPIDEMIOLOGY

The **Institut Pasteur in Iran** collected isolates during several cholera outbreaks in Iran in 2005 and demonstrated that the strains were highly homogenous, revealing the dissemination of a single V. *cholerae* strain[1].

A project linking the **Instituts Pasteur in Morocco**, **Tunis**, and **Algeria** with the **Institut Pasteur** focuses on environmental changes and their effect on choleric and non-choleric vibrions in the Mediterranean basin. For this research, RIIP scientists collaborate with colleagues at the Universities of Verona and Genoa in Italy, as well as the French research agency CNES (Center for Spatial Studies).

GENETIC AND MOLECULAR RESEARCH

Researchers at the **Institut Pasteur in Iran** reported an absence of genetic determinants of virulence in isolates of *V. cholerae* in environmental as compared to clinical isolates[2]. Another study compared the composition of the CTX genetic element of 36 cholera isolates from Iran, showing that variations in content, arrangement, and copy number may occur in isolates belonging to the same clone[3].

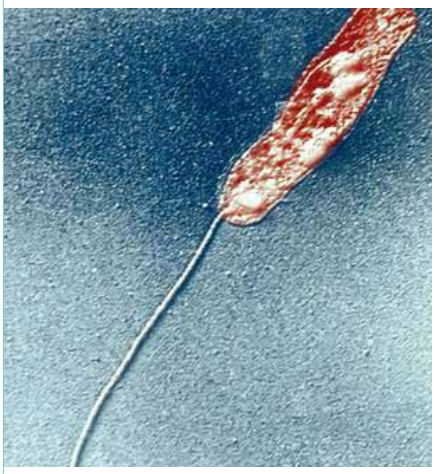
At the **Institut Pasteur**, researchers investigated the glycoconjugate immunogens, finding them to have vibriocidal activity against Ogawa and Inaba strains of cholera, possibly providing clues for the development of a vaccine[4].

DIAGNOSIS, TREATMENT, VACCINE

The **Instituts Pasteur in Paris** and **Madagascar** collaborated to develop a diagnostic test for cholera that is now in widespread use throughout the RIIP.

IN 2008

- ☐ analysis of environmental and clinical isolates for determinants of virulence and indicators of genetic similarity by the Institut Pasteur in Iran
- ☐ confirmation and typing of cholera strains by the CERMES in Niger
- ☐ investigation of the vibriocidal activity of glycoconjugate immunogens by the Institut Pasteur



Cholera vibrion. Colorized image.
© Dodin, A. / Institut Pasteur

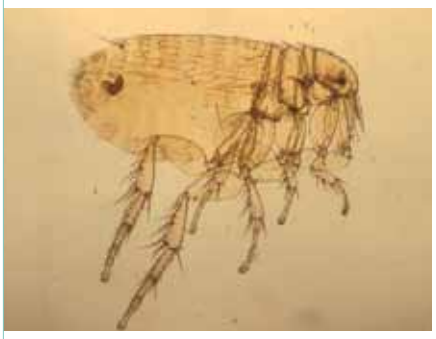
(1) Pourshafie MR et al. "Dissemination of a single Vibrio cholerae clone in cholera outbreaks during 2005 in Iran." *J Med Microbiol.* 2007 Dec; 56(Pt 12): 1615-9.
(2) Bakhshi B et al. "Comparison of distribution of virulence determinants in clinical and environmental isolates of Vibrio cholera." *Iran Biomed J.* 2008 Jul; 12(3): 159-65.
(3) Bakhshi B et al. "Genomic organisation of the CTX element among toxigenic Vibrio cholerae isolates." *Clin Microbiol Infect.* 2008 Jun; 14(6): 562-8.
(4) Grandjean C et al. "Investigation towards bivalent chemically defined gglycoconjugate immunogens prepared from acid-detoxified lipopolysaccharide of Vibrio cholerae O1, serotype Inaba." *Glycoconj J.* 2008 Jul 23 [Epub ahead of print].

Plague

The agent that causes plague, Yersinia pestis, *is one of the most pathogenic bacteria for man. Often considered a "historical" disease, plague is still found in numerous communities around the globe. The recent increase in the number of cases, beginning in the early 1990s, has led scientists to characterize plague as a "re-emerging" disease.*

IN 2008

- ☐ description of epidemiological trends for plague in Madagascar
- ☐ analysis of the virulence of *Y. pestis* with regard to the draining lymph node by researchers at the Institut Pasteur
- ☐ demonstration of the feasibility of using live avirulent *Y. pseudotuberculosis* to inoculate against the plague at the Institut Pasteur



Xenopsylla cheopsis : Flea whose host is the rat. Vector of plague and murine typhus.
© Grenier, P. / Institut Pasteur

EPIDEMIOLOGY

After an outbreak of human plague, the **Institut Pasteur in Algeria** catalogued the infection of *Xenopsylla cheopis* fleas by *Y. pestis*, confirming the zoonotic focus of plague in the country[1].

The **Institut Pasteur in Madagascar**, home to a WHO Collaborating Center for plague, published a study describing the principle epidemiological trends of plague based on 4,473 confirmed or probable cases in the country (1957-2001). The data showed a rising incidence in both rural and urban areas, but with decreasing lethality due to improved control measures[2].

GENETIC AND MOLECULAR STUDIES

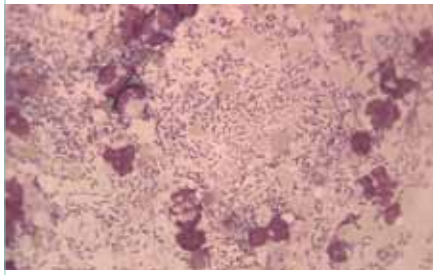
The Yersinia Research unit at the **Institut Pasteur**, a National Reference Center for plague and other Yersinia and a WHO Collaborating Center, has worked extensively on the evolutionary history of plague. In particular, researchers have described the incorporation of an unstable filamentous phage in the genes of the bacillus' ancestor, contributing to its pathogenicity[3]. Another study identified bacterial genes active during septicemic plague in humans by performing a transcriptome analysis[4].

DIAGNOSIS, THERAPY, VACCINE

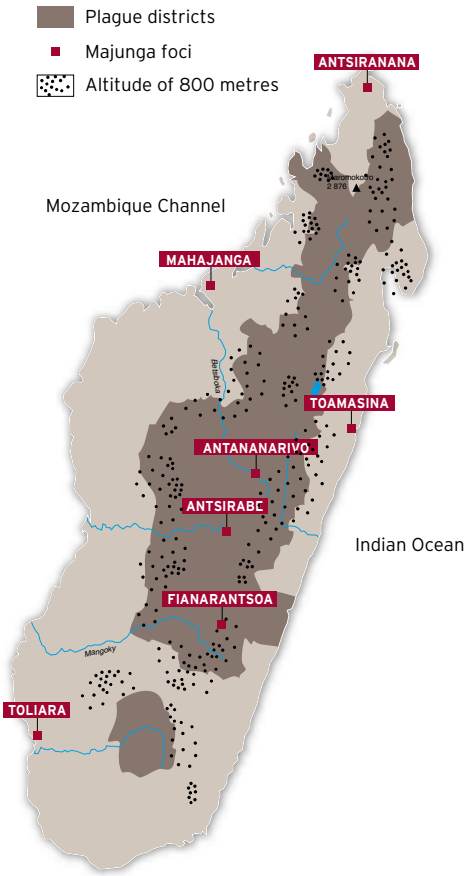
Researchers at the **Institut Pasteur** evaluated the possibility of using *Y. pseudotuberculosis* as a live vaccine against plague. Multiple oral inoculations were found to provide significant protection against plague in mice[5].

IMMUNOLOGY

The **Institut Pasteur** compared disease progression in mice after intradermal inoculation with *Y. pseudotuberculosis* and *Y. pestis* and concluded that the latter's exceptional virulence is associated with its ability to massively infiltrate the draining lymph node without inducing an organized polymorphonuclear cell reaction[6].



Yersinia pestis.
© Mollaret, H.H. / Institut Pasteur



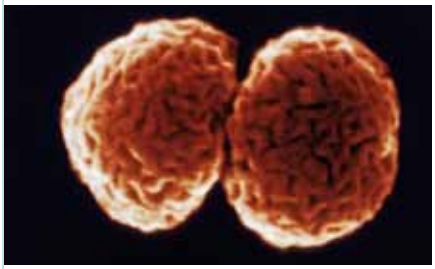
Districts with confirmed or probable plague cases in Madagascar from 1957 to 2001.
Source: Migliana R et al.

(1) Bitam I et al. "Zoonotic focus of plague, Algeria." *Emerg Infect Dis.* 2006 Dec; 12(12): 1975-7.
(2) Migliana R et al. "Epidemiological trends for human plague in Madagascar during the second half of the 20th century: a survey of 20,900 notified cases." *Trop Med Int Health.* 2006 Aug; 11(8): 1228-37.
(3) Derbise A et al. "A horizontally acquired filamentous phage contributes to the pathogenicity of the plague bacillus." *Mol Microbiol.* 2007 Feb; 63(4): 1145-57.
(4) Chauvaux S et al. "Transcriptome analysis of Yersinia pestis in human plasma; an approach for discovering bacterial genes involved in septicaemic plague." *Microbiology.* 2007 Sep; 153(Pt 9): 3112-24.
(5) Blisnick T et al. "Oral vaccination against bubonic plague using a live avirulent Yersinia pseudotuberculosis strain." *Infect Immun.* 2008 Aug; 76(8): 3808-16.
(6) Guinet F et al. "Defective innate cell response and lymph node infiltration specify Yersinia pestis infection." *PLoS ONE.* 2008 Feb 27; 3(2): e1688.

Bacterial meningitis

Several different bacteria can cause meningitis. Of these, Neisseria meningitidis *has the greatest potential to cause epidemics, many of which occur in the African "meningitis belt" extending from Senegal to Ethiopia. Endemic zones also exist in South America and Asia. The disease can kill within hours if not immediately diagnosed and treated.*

Argos project in Niger.



Neisseria meningitidis.
A diplococcus often noted for its a "coffee bean shape". Five to 15% of the population carries it without harmful effects. Four of 13 serotypes are very virulent. Colorized image.
© Riou, J.-Y. ; Service photo / Institut Pasteur

SURVEILLANCE AND PUBLIC HEALTH

Researchers at the **CERMES**, which performs microbiological surveillance for the Ministry of Health, published a study on the rising incidence of meningitis serogroup X in Niger[1]. The CERMES also collaborated with the French National Center for Spatial Studies (CNES) to perform surveillance by means of satellite telecommunications channels (Argos system).

The **Pasteur Center in Cameroon** examined recent microbiological surveillance of meningitis in the northern regions of the country in 2007 and 2008, and noted that all isolates were from serogroup W135, suggesting a lull between epidemic waves[2].

DIAGNOSIS, THERAPY, VACCINE

The **CERMES** in Niger, in association with the **Institut Pasteur**, has developed and patented diagnostic strips for meningococci (serotypes A, C, W135 and Y). An evaluation of these strips in Niger demonstrated that they could be reliably used by non-specialized staff in basic health facilities, who may then recommend vaccination when appropriate[3].

IN 2008

- ☐ evaluation of diagnostic strips for meningococci serotypes A, C, W135 and Y by the Institut Pasteur and the CERMES in Niger
- ☐ study in Bangui on the optimal clinical response to suspected cases of pediatric meningitis

In addition, the **CERMES** will participate in the introduction of the new conjugate vaccine against serogroup A for use in the African "meningitis belt." The project takes place under the aegis of the Meningitis Vaccine Project, a partnership between the WHO and the Program for Appropriate Technology in Health.

Researchers at the **Institut Pasteur**, which houses a National Reference Center for meningococcus, elaborated upon the need for a "universal vaccine" for meningitis that would protect against all serotypes, as well as other strategies to control the disease[4].

CLINICAL RESEARCH

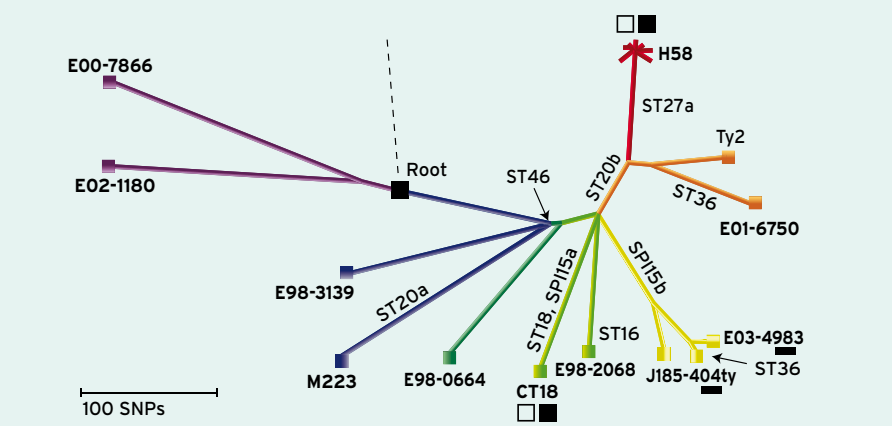
The **Institut Pasteur in Bangui** performed a prospective study of 167 proven or probable cases of pediatric bacterial meningitis[5]. The study's findings shed doubt on the use of ampicillin and chloramphenicol for suspected childhood meningitis and underlined the importance of prompt diagnosis and treatment.

A €1 million grant from the French Ministry of Foreign Affairs created a special research program on meningitis in Africa, which links the **Institut Pasteur**, the **CERMES**, the **Pasteur Center in Cameroon**, and the **Instituts Pasteur in Côte d'Ivoire** and **Bangui.** The project provides capacity building for diagnosis by PCR in collaboration with the **Scientific Institute for Public Health** in Brussels and the French Agency for Preventive Medicine (AMP).

(1) Boisier P et al. "Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in 2006 in Niger." *Clin Infect Dis.* 2007 Mar 1; 44(5): 657-63.
(2) Massenet D et al. "Serogroup W135 meningococcal meningitis, Northern Cameroon, 2007-2008." *Emerg Infect Dis.* 2009 Feb; 15(2): 340-2.
(3) Boisier P et al. "Field evaluation of rapid diagnostic tests for meningococcal meningitis in Niger." *Trop Med Int Health.* 2009 Jan 1; 14(1): 111-117.
(4) Taha MK et al. "Meningococcal vaccines: to eradicate the disease, not the bacterium." *Hum Vaccin.* 2007 Jul-Aug; 3(4): 149-52.
(5) Bercion R et al. "Acute bacterial meningitis at the 'Complexe Pédiatrique' of Bangui, Central African Republic." *J Trop Pediatr.* 2008 Apr; 54(2): 125-8.

Diarrheal diseases

Diarrhea can prove life-threatening for children and immuno-compromised patients such as those suffering from HIV/AIDS. According to the WHO, gastrointestinal infections causing diarrhea kill around 2.2 million people each year, mostly via contaminated food or drinking water or from person to person due to inadequate hygiene.



Phylogenic tree showing different lineages of Samonella enterica *serovar Typhi, by color.*
Source: Holt KE et al.

IN 2008

- ☐ successful completion of a phase II clinical trial for a Shigella vaccine performed by the Institut Pasteur with Inserm and AP-HP
- ☐ identification of common *E. coli* strains in Iran and description of their genetic diversity by the Institut Pasteur in Iran
- ☐ demonstration of the possibility of inoculating against *E. coli* with combined bacterial DNA and proteins by the Institut Pasteur in Iran

Shigella vaccine trial

Researchers at the **Institut Pasteur,** in collaboration with the Inserm and the Paris hospital association (AP-HP), have published results on a phase II clinical trial for an oral vaccine for *Shigella dysenteriae* type 1. Compared to a placebo, the candidate vaccine provided good protection with just one dose, with good tolerance among research subjects. A shigella vaccine would be useful during outbreaks linked to humanitarian disasters (civil wars, refugee situations) and natural catastrophes[7].

SURVEILLANCE AND PUBLIC HEALTH

Researchers at the **Institut Pasteur in Bangui** investigated two dysentery outbreaks and showed them to be caused by two different clones of shigella dysentery type 1. This study, a collaboration between field physicians and microbiologists, will serve as the basis for monitoring the disease over the long term[1].

At the **Institut Pasteur** in Paris, the National Reference Centers for salmonella, and *E. coli* perform regular microbiological surveillance for these pathologies, including the recent identification of a salmonella outbreak in France linked to cheese made from raw milk[2]. Another study evaluated the WHO's Salm-Surv system for antimicrobial susceptibility testing of salmonella around the world. The results showed that laboratories in Central Asia, African and the Middle East are not performing as well as in other regions[3].

EPIDEMIOLOGY

The **Institut Pasteur in Iran** identified the STEC and EPEC strains of *E. coli* as the most important causative agents of diarrhea in Iran[4]. Another study determined that toxigenicity and antibiotic resistance are the main contributing factors to the virulence of Iranian isolates of *E. coli*[5]. A third study of rotavirus strains circulating in Tehran found usual genotypes such as G1P [10] SGI as well as recombinant strains and mixed infections[6]. The **Institut Pasteur in Côte d'Ivoire** detected by RT-PCR the first cases of astrovirus in human diarrheal stools in Abidjan[8]. Additionally, researchers analyzed 642 stools specimens from children younger than 5 years in hospitals and health centers in Abidjan. Findings included a 27.9% prevalence of rotavirus, with higher rates among the youngest

(1) Bercion R et al. "Molecular epidemiology of multidrug-resistant Shigella dysenteriae type 1 causing dysentery outbreaks in Central African Republic, 2003-2004." *Trans R Soc Trop Med Hyg.* 2006 Dec; 100(12): 1151-8.
(2) Dominguez M et al. "Outbreak of Salmonella enterica Serotype Montevideo Infections in France linked to Consumption of Cheese Made from Raw Milk." *Foodborne Pathog Dis.* 2008 Dec 10. [Epub ahead of print]
(3) Hendriksen RS et al. "Results of use of WHO Global Salm-Surv external quality assurance system for antimicrobial susceptibility testing of Salmonella isolates from 2000 to 2007." *J Clin Microbiol.* 2009 Jan; 47(1): 79-85.
(4) Aslani MM et al. "Molecular detection and antimicrobial resistance of diarrheagenic Escherichia coli strains isolated from diarrheal cases." *Saudi Med J.* 2008 Mar; 29(3): 388-92.
(5) Bouzari et al. "Distribution of genes encoding toxins and antibiotic resistance patterns in diarrhoeagenic Escherichia coli isolates in Tehran." *East Mediterr Health J.* 2007 Mar-Apr; 13(2): 287-93.
(6) Farahtaj F et al. "Rotavirus VP7, VP4 and VP6 genotypes co-circulating in Tehran, Iran, between 2004 and 2004." *Epidemiol Infect.* 2007 Jul; 135(5): 834-8.
(7) Launday O et al. "Safety and immunogenicity of SC599, an oral live attenuated Shigella dysenteriae type-1 vaccine in healthy volunteers: results of a phase 2, randomized, double-blind placebo controlled trial." *Vaccine.* 2009 Jan 7 [Epub ahead of print].
(8) Bini JC et al. "[Detection by RT-PCR of the 1st cases of Astrovirus in human stools in Abidjan, Côte d'Ivoire]." *Bull Soc Pathol Exot.* 2007 Oct; 100(4): 243-5.

children, and an unequal distribution of the various P genotypes[9].

GENETIC AND MOLECULAR STUDIES

Researchers in the Laboratory for Enteric Bacterial Pathogens at the **Institut Pasteur** published an article on the phylogenic tree of *Salmonella enterica* serovar Typhi, reporting patterns of genetic isolation and drift. This finding is consistent with the proposed role of asymptomatic carriers of Typhi as the main reservoir of this pathogen[10].

Researchers at the **Cantacuzino Institute** in Romania are developing PCR-based methods for detecting *E. coli* verotoxin-producing strains, noroviruses, rotaviruses, campylobacter and crypotosporidium as etiolic agents of diarrhea.

DIAGNOSIS, THERAPY, VACCINE

Researchers at the **Institut Pasteur** developed a dipstick test for rapid diagnosis of *Shigella flexneri 2a* in stool that is capable of detecting even highly diluted samples with very high specificity. Sensitivity has been improved by individually packaging dipsticks in waterproof bags[11].

In a collaboration with the Total industrial group, researchers at the **Instituts Pasteur in Bangui** and **Madagascar** are currently investigating ways to improve diagnostic and treatment strategies for diarrhea in children, including proper reception and follow-up.

IMMUNOLOGY

The **Institut Pasteur in Iran** published a study underlining the danger of crytosporidiosis, a potentially fatal diarrheal infection, for immuno-compromised patients[12]. Another study of Enteroaggregative *E. coli* (EAEC) demonstrated the possibility of using bacterial DNA and proteins to vaccinate against the infection in a mouse model[13].

Researchers at the **Institut Pasteur in Lille** developed a model using adult severe combine immunodeficiency mice to study cryptosporidiosis. This model allowed for the association of *C. parvum* to the formation of polyps and adenocarcinoma lesions in mice treated with Dexamethasone[14].

BASIC RESEARCH

The **Institut Pasteur in Iran** demonstrated the genetic diversity of *E. coli* strains producing cytolethal distending toxin, suggesting an independent acquisition of virulence genes, for example via horizontal gene transfer[15].

Colibri

Colibri is a searchable database of the complete DNA and protein sequences derived from the paradigm strain E. coli K-12. Researchers can easily browse data and retrieve information, using various criteria (gene names, location, keywords, etc.).
http://genolist.pasteur.fr/Colibri/

Rotavirus of bovine origin. Rotaviruses are responsable for 70% of cases of acute diarrhea in children and 30-50% of hospitalizations for pediatric gastroenteritis worldwide. Colorized image.
© Dauguet, C. / Institut Pasteur

Escherichia coli undergoing cell division (enlargement X 20,000). Colorized image.
© Ryter, A. / Institut Pasteur

Institut Pasteur in Côte d'Ivoire.

(9) Akoua-Koffi C et al. "[Epidemiological and virological aspects Rotavirus diarrhoea in Abidjan, Côte d'Ivoire (1997-2000)]." *Bull Soc Pathol Exot.* 2007 Oct; 100(4): 246-9.
(10) Holt KE et al. "High-throughput sequencing provides insights into genome variation and evolution in Salmonella Typhi." *Nat Genet.* 2008 Aug; 40(8): 987-96.
(11) Nato F et al. "Dipstick for rapid diagnosis of Shigella flexneri 2a in stool." *PLoS ONE.* 2007 Apr 18; 2(4): e361.
(12) Nahrevanian H et al. "Cryptosporidiosis in immunocompromised patients in the Islamic Republic of Iran." *J Microbiol Immunol Infect.* 2008 Feb; 41(1): 74-7.
(13) Bouzari et al. "Immune response against adhesins of enteroaggregative Escherichia coli immunized by three different vaccination strategies (DNA/DNA, protein/protein, and DNA/protein) in mice." *Comp Immunol Microbiol Infect Dis.* 2008 Nov 18. [Epub ahead of print]
(14) Certad G et al. "Cryptosporidium parvum, a potential cause of colic adenocarcinoma." *Infect Agent Cancer.* 2007 Nov 21; 2: 22.
(15) Oloomi M et al. "Molecular profile and genetic diversity of cytolethal distending toxin (CDT)-producing Escherichia coli isolates from diarrheal patients." *APMIS.* 2008 Feb; 116(2): 125-32.

Leptospirosis

One of the world's most common zoonotic diseases, leptospirosis infects humans when they come into contact with water contaminated by animal urine, such as in city slums and rural agricultural environments. Mortality rates are significant, due primarily to difficulties diagnosing the disease, the lack of a human vaccine, and complicated treatment regimes.

IN 2008

- ☐ proof of the ability of leptospires to form biofilms under certain conditions by researchers at the Institut Pasteur
- ☐ first sequencing of a Leptospira genome (*L. biflexa*) at the Institut Pasteur
- ☐ creation of a library of Leptospira mutants using the mariner-based transposon Himar1 in a collaboration between the Institut Pasteur and Fiocruz in Brazil

SURVEILLANCE AND PUBLIC HEALTH

The **Institut Pasteur in New Caledonia** performs laboratory surveillance on leptospirosis and has described epidemiological and biological features of the disease in the territory, including an incidence of 21 cases per 100,000 and a lethality rate of 5.4%[1]. Another study confirmed the widespread presence of human leptospirosis in various Pacific island states and identified predominant subgroups that suggest a rodent reservoir[2].

The **Institut Pasteur** houses a National Reference Center for leptospirosis. This center participates in a project on the epidemiology and diagnosis of leptospirosis and various other diseases in Madagascar.

DIAGNOSIS, THERAPY, VACCINE

A collaborative project led by the **Institut Pasteur in New Caledonia** focuses on designing and evaluating a rapid diagnostic test for leptospirosis, allowing for the rapid biological confirmation of infection in blood or urine samples.

The **Institut Pasteur in Iran** devised a technique using PCR-RFLP to detect and differentiate pathogenic and nonpathogenic leptospira[3].

GENETIC AND MOLECULAR STUDIES

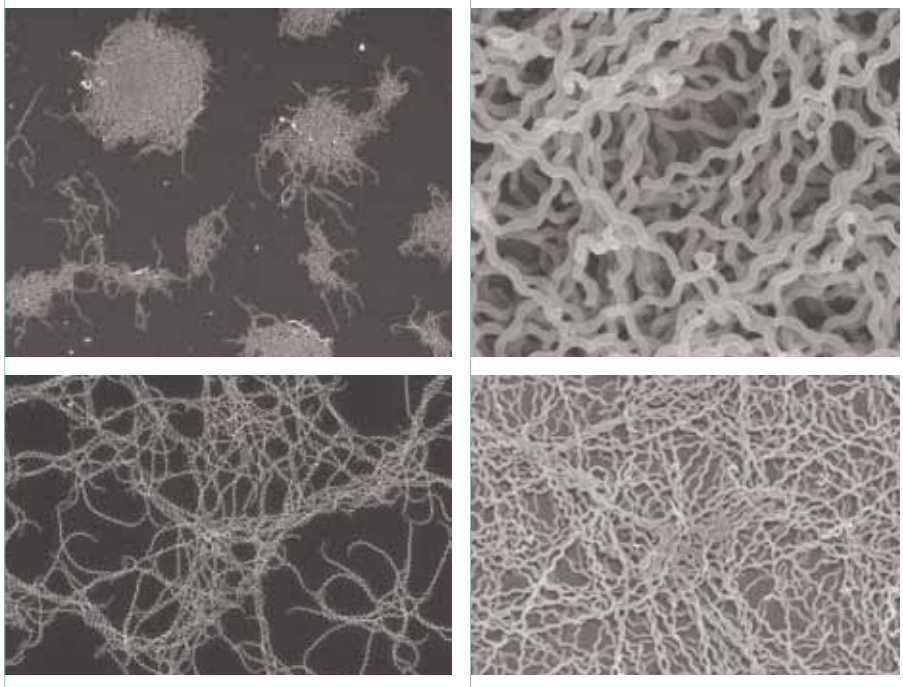
The **Institut Pasteur** sequenced the genome of *L. biflexa*, making it the first saprophytic leptospira to be sequenced, providing insights on the genus' evolution[4].

The **Institut Pasteur** and **Fiocruz**, among other partners, developed the mariner-based transposon Himar1 to generate the first mutants in *Leptospira interrogans*, the most common cause of leptospirosis in humans and animals. This library represents a valuable resource for the study of leptospirosis and the genes contributing to its virulence[5].

Researchers at the **Institut Pasteur** also reported, for the first time, a protein called Loa22 that is essential to the virulence of *Leptospira interrogans*[6].

BASIC RESEARCH

The Unit on Spirochete Biology at the **Institut Pasteur** reported the ability of leptospires to create biofilms, possibly helping them to survive in the environment and colonize the host (see image)[7].



Leptospires forming biofilms. Unit on Spirochete Biology at the Institut Pasteur.

(1) Berlioz-Arthaud A et al. "[Laboratory based human leptospirosis surveillance in New Caledonia (2001-2005)]." *Bull Soc Pathol Exot.* 2007 May; 100(2): 133-8.
(2) Berlioz-Arthaud A et al. "Multicentre survey of incidence and public health impact in the Western Pacific." *Trans R Soc Trop Med Hyg.* 2007 Jul; 101(7): 714-721.
(3) Djadid ND et al. A simple and rapid nested polyerase chain reaction-restriction fragment length polymorphism technique for differentiation of pathogenic and nonpathogenic Leptospira spp. *Diagn Microbiol Infect Dis.* 2008 Dec 19. [Epub ahead of print]
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(5) Murray GL et al. "Genome-transposon mutagenesis in pathogenic Leptospira spp." *Infect Immun.* 2008 Dec 1. [Epub ahead of print]
(6) Ristow P et al. "The Omp-A-like protein Loa22 is essential for leptospiral virulence." *PLoS Pathog.* 2007 Jul; 3(7): e97.
(7) Ristow P et al. "Biofilm formation by saprophytic and pathogenic leptospires." *Microbiology.* 2008 May; 154(Pt 5): 1309-17.

Helicobacter pylori

At least half of the world's population is infected with Helicobacter pylori, *and though most of cases are asymptomatic, the bacterium is a major cause of diseases of the upper gastrointestinal tract. The route of transmission remains unknown but most infections are acquired during childhood, and infection rates are higher in developing countries. No vaccine currently exists.*

IN 2008

- ☐ demonstration of the cost effectiveness and comparable accuracy of homemade ELISA kits to diagnose *H. pylori* infection by the Institut Pasteur in Iran
- ☐ determination of the prevalence of the cagA gene in bacterial samples in Iran
- ☐ proof of genetic susceptibility to diseases of the upper gastrointestinal tract in the presence of *H. pylori* by the Institut Pasteur in Iran

EPIDEMIOLOGY

A project bringing together **the Instituts Pasteur in Algeria, Cambodia, Madagascar, Dakar, Greece,** and Paris aims to gauge the frequency of infection by *H. pylori* in patients with gastro-duodenal pathologies. The project also examines susceptibility to antibiotics and genetic diversity of the cytotoxin-associated gene A (cagA).

DIAGNOSIS, THERAPY, VACCINE

The **Institut Pasteur in Iran** published a study advocating the use of home-made ELISA kits using soluble antigenic fractions of *H. pylori* proteins. The homemade kit had comparable sensitivity/specificity values, as well as a significant cost benefit[1].

H. pylori and human migrations

Scientists have long understood that the Pacific was peopled in two waves – first, New Guinea and Australia; then Melanesia and Polynesia some 20,000 years later. Now, archeological and linguistic proof has been supplemented by research conducted by a network of scientists at the **Instituts Pasteur** in Paris and **New Caledonia** and elsewhere. These partners analyzed strains of *H. pylori* using Bayesian assignment analysis, demonstrating that global patterns of migration are mirrored in their genomes due to founder effects and subsequent geographic isolation[11].

GENETIC AND MOLECULAR STUDIES

The **Institut Pasteur** participates in the HELDIVNET project supported by the European Era-Net platform. The project aims to broaden researchers' understanding of *H. pylori's* genetic diversity, as well as the role of human genetic variation in determining susceptibility to infections (see text box).

In contrast with previous findings, a study performed by the **Institut Pasteur in Iran** showed no association between possession of the dupA gene and increased risk of duodenal ulcer or decreased risk of gastric cancer after infection by *H. pylori*[2]. Another study confirmed, via genotyping and serology analysis, that the majority of Iranian strains of *H. pylori* are positive for the cagA gene[3].

The **Institut Pasteur in Greece** also studied the cagA gene, and proposed a strategy to determine cagA motifs in clinical strains based on a one-step PCR modification[4].

IMMUNOLOGY

The **Institut Pasteur** determined that certain types of immune response to infection by *H. pylori,* specifically up-regulation of the gene IL-23p19, may promote the severity of gastric lesions[5].

BASIC RESEARCH

Researchers at the **Institut Pasteur** demonstrated the central role of trans-translation in *H. pylori* both for ribosome rescue and for protein degradation, which may prove a target for the development of new antibiotics[6].

Another team at the **Institut Pasteur** developed systems to engineer conditional mutants of essential genes of *H. pylori*[7]. The same team published numerous articles on *H. pylori,* demonstrating for the first time the induction of NF-kappaB activation in murine gastric mucosal cells during acute *H. pylori* infection[8]. Other studies highlighted the importance of channel-mediated potassium uptake[9] and genes coding for carbonic anhydrases[10] in *H. pylori* for efficient gastric colonization.

PyloriGene

PyloriGene is a searchable database of the complete DNA and protein sequences derived from the 26695 and J99 strains of *H. pylori.* Researchers can easily browse data and retrieve information, using various criteria (gene names, location, keywords, etc.). http://genolist.pasteur.fr/PyloriGene/

(1) Mohammadi M et al. "Advantage of using home-made ELISA kits for detection of Helicobacter pylori infection over commercially imported kits." *Indian J Med Microbiol.* 2008 Apr-Jun; 26(2): 127-31.
(2) Douraghi M et al. "dupA as a risk determinant in Helicobacter pylori infection." *J Med Microbiol.* 2008 May; 57(Pt 5): 554-62.
(3) Talebkhan Y et al. "cagA gene and protein status among Iranian Helicobacter pylori strains." *Dig Dis Sci.* 2008 Apr; 53(4): 925-32.
(4) Panayotopoulou EG et al. "Strategy to characterize the number and type of repeating EPIYA phophorylaton motifs in the carboxyl terminus of CagA protein in Helicobacter pylori clinical isolates." *J Clin Microbiol.* 2007 Feb; 45(2): 488-95.
(5) Vivas JR et al. "Interferon gamma-signature transcript profiling and IL-23 upregulation in response to Helicobacter pylori infection." *Int J Immunopathol Pharmacol.* 2008 Jul-Sept; 21(3): 515-26.
(6) Thibonnier M et al. "Trans-translation in Helicobacter pylori: essentiality of ribosome rescue and requirement of protein tagging for stress resistance and competence." *PLoS ONE.* 2008; 3(11): e3810.
(7) Boneca IG et al. "Development of inducible systems to engineer conditional mutants of essential genes of Helicobacter pylori." *Appl Environ Microbiol.* 2008 Apr; 74(7): 2095-102.
(8) Ferrero RL et al. "NF-kappaB activation during acute Helicobacter pylori infection in mice." *Infect Immun.* 2008 Feb; 76(2): 551-61.
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PARASITIC DISEASES

To learn more about research on diseases at the Institut Pasteur – too extensive to be detailed here – visit:
www.pasteur.fr

Malaria

One of the world's largest pandemic diseases, malaria kills 1 to 3 million people per year, almost all of them in the tropical and developing world. No vaccine currently exists against this parasite, which is a leading cause of death for children under 5.

EPIDEMIOLOGY

Researchers at the **Institut Pasteur in Cambodia** published an epidemiological study of malaria in Cambodia, enrolling over 11,000 individuals in the Sampovloun, Koh Kong and Preah Vihear areas[1]. The study provided a much more complex picture of the situation than had been previously been available, including a heterogeneous distribution of prevalence rates and *Plasmodium* species, as well as a large asymptomatic reservoir.

The **Institut Pasteur in Madagascar** published a review of six decades of widespread chloroquine use in Madagascar, concluding that the drug was effective early on but recommending artemisinin-based combination therapies for the future[2].

Artemisinin-based combination therapy seems to have proved effective in the Dielmo and Ndiop regions of Senegal, where initial data from epidemiological studies undertaken by the **Institut Pasteur in Dakar** shows 68% and 80% fewer malaria attacks respectively since the implementation of this therapy in 2001.

DIAGNOSTIC AND THERAPEUTIC TOOLS

The **Institut Pasteur in Madagascar** assessed the accuracy of various diagnostic measures, including conventional microscopy, which proved the most accurate, followed by various rapid diagnostic tests, as compared to the "gold standard" of RT-PCR[3].

GENETIC AND MOLECULAR STUDIES

The **Institut Pasteur in Bangui** published a study providing the first estimates of the genetic diversity and genotype multiplicity of *P. falciparum* infections in residents of Bangui[4]. The results showed a very high level of polymorphism, as well as variations within the city of Bangui.

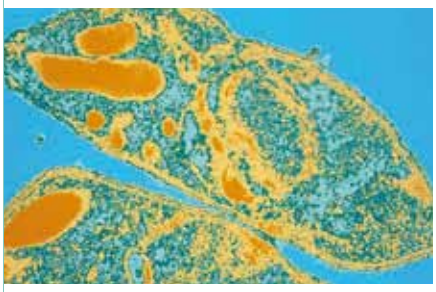
Vaccine Research

The Biomedical Parasitology Unit at the **Institut Pasteur** is involved in research to develop two potential vaccines, one based on molecules present on the parasite during the blood cycle, and another during the hepatic stage. The former molecule has been tested in a phase I clinical trial in Europe and Africa, where it proved to be safe, immunogenic and protective. Trials of the other molecules are currently underway.

IN 2008

- ☐ evaluation of the accuracy of various diagnostic techniques in Madagascar
- ☐ first estimates of the genetic diversity of *Plasmodium falciparum* from isolates collected in Bangui
- ☐ analysis of the immune response to infection in pregnant women, specifically regarding dendritic cells, at the Institut Pasteur in Dakar
- ☐ demonstration of *Anopheles*' response to environmental change in Senegal

In a collaborative project, researchers at the **Instituts Pasteur in Madagascar** and **Cambodia** and the **CERMES** in Niger are working on applying molecular markers to study the response of *P. falciparum* to derivatives of artemisinin and other molecules in the treatment combination used in these countries.



Plasmodium falciparum.
© Institut Pasteur

(1) Incardona S et al. "Large-scale malaria survey in Cambodia: novel insights on species distribution and risk factors." *Malar J.* 2007 Mar 27; 6:37."
(2) Randrianarivelojosia M et al. "Lessons learnt from the six decades of chloroquine use (1945-2005) to control malaria in Madagascar." *Trans R Soc Trop Med Hyg.* 2009 Jan; 103(1): 3-10.
(3) Rakotonirina H et al. "Accuracy and reliability of malaria diagnostic techniques for guiding febrile outpatient treatment in malaria-endemic countries." *Am J Trop Med Hyg.* 2008 Feb; 78(2): 217-21.
(4) Domazon V et al. "Genetic diversity and genotype multiplicity of *Plasmodium falciparum* infections in symptomatic individuals living in Bangui (CAR)." *Acta Trop.* 2008 Jul; 107(1): 37-42.
(5) Pierrot C et al. "Contribution of T cells and neutophils in protection of young susceptible rats from fatal experimental malaria." *J Immunol.* 2007 Feb 1; 178(3): 1713-22.

IMMUNOLOGY

The **Institut Pasteur in Lille** analyzed the mechanisms involved in age-dependent protection against malaria. Researchers demonstrated that transferring spleen cells from infected but asymptomatic adult rats could provide protection to younger rats, possibly due to the transfer of T cells [5].

In Paris, the **Center for the Production and Infection of** *Anopheles* (CEPIA) produces over a million female mosquitoes a year to enable researchers to study the interactions between the parasites responsible for malaria and their hosts.

Institut Pasteur in Côte d'Ivoire.
© *Grison, J.*

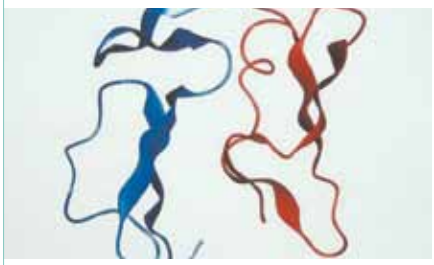
At the **Institut Pasteur in Dakar**, researchers demonstrated decreased levels of dendritic cells in pregnant women infected with malaria, possibly triggering alterations in the immune response to the pathogen [6].

ENTOMOLOGY

The **Institut Pasteur – Cenci Bolognetti Foundation** developed a new approach to analyzing genetic differentiation within *Anopheles gambiae* subspecies [7]. Another study on *Anopheles* in the Gambia River basin concluded that M-form mosquitoes fare better in marshy areas whereas S-form mosquitoes prefer free-draining soil, evidence of ecological divergence between these two forms of *Anopheles* [8]. Finally, researchers studied two genetic mutations conferring resistance to insecticides (DDT and pyrethroids) in *Anopheles gambiae*, and found them to be widespread in west and west-central Africa [9].

In a collaboration between the **CERMES** in Niger and the **Instituts Pasteur in Cambodia** and **Madagascar**, the "Modipop" project aims to induce genetic changes in vector mosquitoes to prevent or mitigate transmission of *Plasmodium* to humans.

Researchers at the **Institut Pasteur in Dakar** documented changes in vector bionomics and malaria epidemiology following the construction of two dams in the Senegal River [10]. Another study determined upper and lower limits for the concentration of *Plasmodium* gametocytes, in order for man-to-mosquito transmission to occur [11].



Structure of a potential vaccine against malaria: the protein Msp-1's C-terminal fragment of *Plasmodium*

Vector control in French Guiana © *IP Guyane française / Institut Pasteur*

CLINICAL STUDIES

The **Institut Pasteur in Madagascar** reported enhanced efficacy of amodiaquine compared to chloroquine in patients 5 years or older with uncomplicated malaria, and therefore recommend its use in combination with other anti-malarial drugs [12].

Researchers at the **Institut Pasteur in Côte d'Ivoire** described the biological mechanisms causing anemia in malaria patients in tropical urban areas [13]. Another study tested the efficacy of co-formulated fixed dose combination therapy over 24 hours and found it comparable to giving the same medicine in 3 doses over 3 days [14].

Each year, the **Institut Pasteur in Madagascar** offers a 6-week French-language "Malaria Workshop" that teaches health professionals to fight malaria more efficiently in endemic countries. The course focuses on problem-based learning, emphasizes sharing between participants and tutors, and promotes the use of the Internet to seek out documentation.

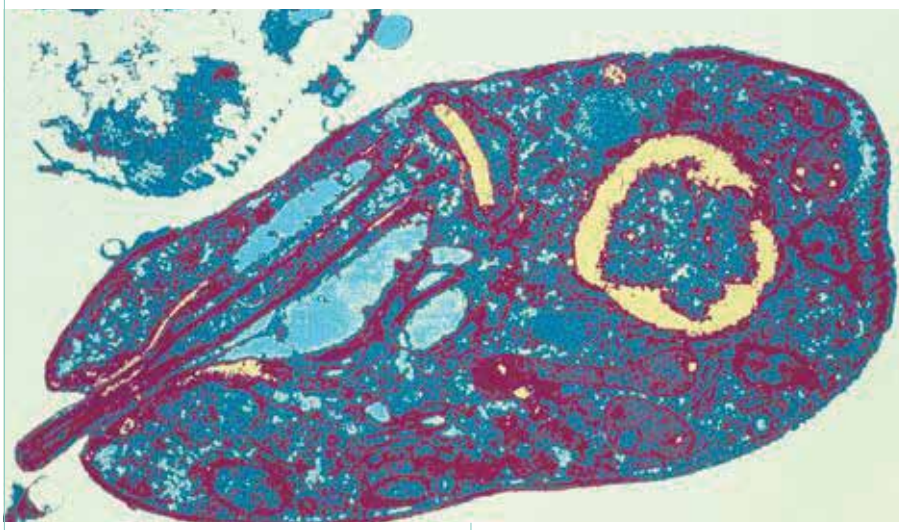
(6) Diallo M et al. "Decrease of lymphoid dendritic cells in blood from malaria-infected pregnant women." *Int J Parasitol.* 2008 Jun 4. [Epub ahead of print.]
(7) Santolamazza F et al. "Insertion polymorphisms of SINE200 retrotransposons within speciation islands of Anopheles gambiae molecular forms." *Malar J.* 2008 Aug 25; 7: 163.
(8) Caputo B et al. "Anopheles gambiae complex along The Gambia river, with particular reference to the molecular forms of An. Gambiae s.s." *Malar J.* 2008 Sept 22; 7: 182.
(9) Santolazza F et al. "Distribution of knock-down resistance mutations in Anopheles gambiae molecular forms in west and west-central Africa." *Malar J.* 2008 Apr 29; 7:74.
(10) Dia I et al. "Bionomics of malaria vectors and relationship with malaria transmission and epidemiology in three physiographic zones in the Senegal River Basin." *Acta Trop.* 2008 Feb; 105(2): 145-53.
(11) Paul RE et al. "Aggregation in malaria parasites places limits on mosquito infection rates." *Infect Genet Evol.* 2007 Sept; 7(5): 577-86.
(12) Randriamanantena A et al. "[Therapeutic efficacy of amodiaquine against uncomplicated malaria in Madagascar.]" *Santé.* 2007 Apr-Jun; 17(2): 75-8.
(13) Ahiboh et al. "[Anaemia, iron index status and acute phase proteins in malaria (Abidjan, Côte d'Ivoire)]." *Bull Soc Pathol Exot.* 2008 Feb; 101(1): 25-8.
(14) Penali LK et al. "Single-day, three-dose treatment with fixed dose combination artesunate/sulfamethoxypyrazine/pyrimethamine to cure *Plasmodium* falciparum malaria." *Int J Infect Dis.* 2008 Jul; 12(4): 430-7.

Leishmaniasis

Leishmaniasis is caused by protozoan parasites transmitted by sand flies native to tropical and sub-tropical regions, most notably the Maghreb and the Middle East. There are three subtypes of varying severity, with symptoms ranging from unsightly sores to damage to the spleen or liver, and sometimes death. No vaccine currently exists, despite recent work on a number of candidate vaccines.

IN 2008

- ☐ development of a new rapid, sensitive diagnostic test for *L. donovani* by the Institut Pasteur in Greece
- ☐ new analysis of the risk for outbreaks in southern Europe in a partnership between the Instituts Pasteur in Paris and Algeria
- ☐ preliminary tests of candidate vaccines in Iran and Tunisia



Amastigote of *Leishmania mexicana amazonensis* in cross-section. Causal agent of leishmaniasis in the New World. (Enlargement x 40,000). Colorized image.

SURVEILLANCE AND PUBLIC HEALTH

The **Institut Pasteur in Tunis** is home to a WHO Collaborating Center for Leishmaniasis, where researchers are currently performing spatial surveillance to better understand the links between environmental changes caused by global warming and the evolution of the disease in Tunisia.

In Athens, the **Institut Pasteur in Greece**, home to a Regional Reference Laboratory for the disease, has recently published studies warning of the emergence of new strains in southern Europe, where *L. infantum* is already endemic[1], and genetically classifying *L. infantum* into three geographic sub-groups[2].

These two institutes, along with the **Instituts Pasteur in Paris** and **Algeria**, also participate in **Leish-Med**, a European Commission project that performs monitoring of risk factors for leishmaniasis in the Mediterranean basin.

The **Institut Pasteur in Iran** investigated the cause of infantile visceral leishmaniasis in northwestern Iran and discovered a widespread distribution of *L. tropica* in sandflies, a species seemingly imported from elsewhere in the Middle East[3].

GENETIC AND MOLECULAR STUDIES

The **Institut Pasteur in Algeria** documented polymorphisms and genetic variability in 55 strains of *L. infantum* from Algeria[4].

Researchers at the **Institut Pasteur in Tunis** used a technique called serial analysis of gene expression (SAGE) to examine interaction between *L. major* and human macrophages[5]. They discovered that the parasite modulates key transcripts in human macrophages in order to survive in the host.

In Brazil, **Fiocruz** examined isolates of patients with rare clinical manifestations of the disease using molecular markers and demonstrated the utility of the latter in researching genetic variability of the parasite[6].

DIAGNOSTIC AND THERAPEUTIC TOOLS

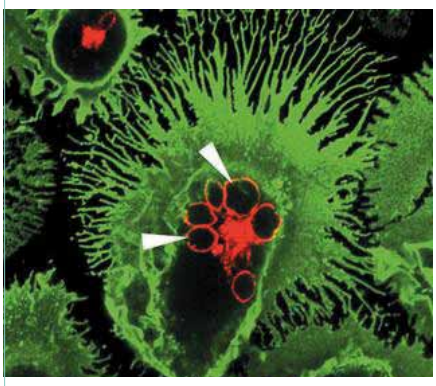
The **Institut Pasteur in Greece** developed a simple, rapid, sensitive, and cost-effective diagnostic test for *L. donovani* complex strains causing visceral leishmaniasis[7]. This assay allowed for the first identification of *L. donovani* causing viscerotropic and/or dermotropic leishmaniasis in Europe[8].

(1) Dujardin JC et al. "Spread of vector-borne diseases and neglect of Leishmaniasis, Europe." *Emerg Infect Dis.* 2008 Jul; 14(7): 1013-8.
(2) Kuhls et al. "Differentiation and Gene Flow among European Populations of Leishmania infantum MON-1." *PLoS Negl Trop Dis.* 2008 Jul 9; 2(7): e261.
(3) Parvizi et al. "Two Leishmania species circulating in the Kaleybar focus of infantile visceral leishmaniasis, northwest Iran: implications for deltamethrin dog collar intervention." *Trans R Soc Trop Med Hyg.* 2008 Sept; 102(9): 891-7.
(4) Seridi N et al. "Genetic polymorphism of Algeria Leishmania infamntum strains revealed by multilocus microsatellite analysis." *Microbes Infect.* 2008 Oct; 10(12-13): 1309-15.
(5) Guerfali FZ et al. "Simultaneous gene expression profiling in human macrophages infected with Leishmania major parasites using SAGE." *BMC Genomics.* 2008 May 21; 9: 238.
(6) Baptista C et al. "Leishmania (Viannia) braziliensis genotypes identified in lesions of patients with atypical or typical manifestations of tegumentary leishmaniasis: Evaluation by two molecular markers." *Exp Parasitol.* 2008 Dec 16. [Epub ahead of print]
(7) Haralambous C et al. "Development of a molecular assay specific for the Leishmania donovani complex that discriminates L. donovani/Leishmania infantum zymodemes: a useful tool for typing MON-1." *Diagn Microbiol Infect Dis.* 2008 Jan; 60(1): 33-42.
(8) Antoniou M et Al "Leishmania donovani leishmaniasis in Cyprus." *Lancet Infect Dis.* 2008 Jan; 8(1): 6-7.

Researchers in Athens also determined the antileishmanial activity of a compound derived from the European yew tree, and found it to selectively inhibit the growth of *L. donovani* intracellular amastigotes[9].

The European Commission project (FP-7) **Leish-Drug** brings together the **Instituts Pasteur in Montevideo, Paris, Tunis**, and **Korea** with the goal of developing new therapeutic tools to fight leishmaniasis.

The **Institut Pasteur** performed a study to optimize a new topical therapy of aminoglycosides for localized cutaneous leishmaniasis, and found that occlusive dressing significantly increased parasitological and clinical efficiency of the treatment in mice[10].



Detection by immunofluorescence of class II molecules (in green) and H-2M molecules (in red) in murine dentritic cells infected by *L. amazonensis*.
The *Leishmania* parasites are indicated by the white arrows.
© Prina, E. ; Unité d'Immunophysiologie et parasitisme intracellulaire / Institut Pasteur

IMMUNOLOGY

The **Institut Pasteur in Tunis** compared the capacity of various *L. major* strains to infect and modulate cytokine production in human monocytes derived from peripheral blood[11]. In another study, researchers identified all parasitic proteins in the *L. major* proteome that interact with CD8 T cells[12].

The **Institut Pasteur in French Guiana** proposed an immunological timeline for patients infected with *L. guyanensis*, beginning with the production and circulation of interferon-gamma and T cell receptors in the bloodstream, followed by migration to the infection site on the skin[13].

VACCINE RESEARCH

The **Institut Pasteur in Tunis** tested four DNA-based candidate vaccines for leishmaniasis, each of which offered partial but not full protection in mice. By creating vaccine "cocktails" of various plasmids encoding to immuno-dominant *Leishmania* antigens, researchers were able to improve protection but still fell short of total efficacy[14].

The **Institut Pasteur in Iran** tried a different tack, demonstrating the protective effect of an *L. infantum* protein by using a prime boost approach[15].

In Brazil, researchers at **Fiocruz** identified a candidate antigen for vaccine development against visceral leishmaniasis[16] and described the partial protective immunity conferred by the antigen in beagle dogs[17].

ENTOMOLOGY

The **Institut Pasteur in Iran** studied the transmission cycles of *Leishmania* in Iranian sandflies and noted the heretofore unexpected presence of species such as *L. turanica*. Though non-pathogenic for humans, this species could alter the efficacy of vaccines against *Leishmania*[18].

Cutaneous leishmaniasis, so-called "Old World" type: wound on the leg caused by *L. major, L. tropica* or *L. aethiopica*. Africa is the most affected continent.
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Cutaneous leishmaniasis on the hand, in Medellin, Colombia.
© Rodhain, F. / Institut Pasteur

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(11) Meddeb-Garnaoui A et al. "Effects of tropisms and virulence of Leishmania parasites on cytokine production by infected human monocytes." *Clin Exp Immunol.* 2008 Nov 20. [Epub ahead of print]
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(15) Khoshgoo N et al. "Cysteine proteinase type III is protective against Leishmania infantum infection in BALB/c mice and highly antigenic in visceral leishmaniasis individuals." *Vaccine.* 2008 Oct 29; 26(46): 5822-9.
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(17) Fernandes AP et al. "Protective immunity against challenge with Leishmania (Leishmania) chagasi in beagle dogs vaccinated with recombinant A2 protein." *Vaccine.* 2008 Oct 29; 26(46): 5888-95.
(18) Parvizi P et al. "Nested PCRs and sequencing of nuclear ITS-rDNA fragments detected three Leishmania species of gerbils in sandflies from Iranian foci of zoonotic cutaneous leishmaniasis." *Trop Med Int Health.* 2008 Sep; 13(9): 1159-71.

Trypanosomiasis

Trypanosomiasis is a parasitic disease that exists in two forms: the Latin American form, called Chagas' disease, and the more prevalent African form, known as sleeping sickness. In both diseases, initial symptoms are mild, but long-term infections can be fatal. Both diseases have insect vectors and no vaccine currently exists.

IN 2008

- ☐ analysis of the ecology and epidemiology of *Trypanosoma* with regard to its vector in Brazil by Fiocruz
- ☐ basic research on flagellum length in trypanosomes and its effect on cell entry and exit at the Institut Pasteur
- ☐ identification of risk factors for cardioembolic ischemic stroke for patients with Chagas' disease in Brazil
- ☐ analysis of the life cycle of *T. cruzi* by the Institut Pasteur in Montevideo

EPIDEMIOLOGY

In Brazil, **Fiocruz** has published extensively on Chagas' disease, including papers on the epidemiology of Chagas' disease in various regions of Brazil and the transmission cycle among wild and domestic animals[1].

GENETIC AND MOLECULAR STUDIES

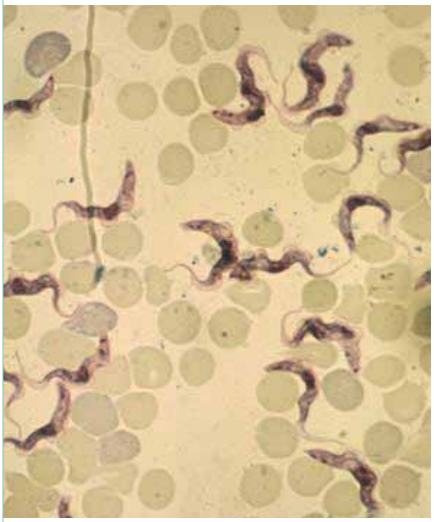
Researchers at **Fiocruz** studied the metabolism of *Trypanosoma cruzi* and identified over 700 proteins necessary or helpful to the parasite's survival in the host[2].

BASIC RESEARCH

The **Institut Pasteur** published a study on flagellum length in trypanosomes, suggesting a link to the function of the flagellar pocket, sole site for endocytosis and exocytosis[3]. Another study focused on characterizing an essential enzyme (PRAC) of *T. cruzi*, which is a validated therapeutic target for Chagas' disease[4].

The **Institut Pasteur in Montevideo** studied the life cycle of *T. cruzi*, particularly the alternation between replicative/non-infective forms to non-replicative/infective forms[5].

Researchers at **Fiocruz** demonstrated that treating *Trypanosoma*-infected mice with an antagonist of certain immune functions can reduce damage to cardiac tissue[6].



Trypanosoma brucei gambiense in human blood. Trypanosomiasis is an endemic disease in Africa, where it is spread by the tsetse fly.
© Lamy, L. / Institut Pasteur

IMMUNOLOGY

Researchers at **Fiocruz** in Brazil are working on various immunological aspects of *Trypanosoma* infections. They have demonstrated that the alpha-2-macroglobulin limits apoptosis in both host cells and parasites[7], and that recombinant antigens of *T. cruzi* are capable of inducing a T helper type 1 immune response in some Chagas patients[8]. They also described the initial cellular events following *T. cruzi* recognition by TLR9 in dendritic cells[9].

ENTOMOLOGY

At **Fiocruz**, researchers published a study on the ecology and epidemiology of *Trypanosoma* in the context of its vector, the blood-sucking assassin bug (*Triatominae*)[10]. Another study attempted to understand sub-divisions in the species *Triatoma brasiliensis* and reinforced the hypothesis that the complex consists of two species and two subspecies[11].

CLINICAL RESEARCH

Fiocruz researchers performed a study on 1,043 patients with Chagas' disease, and identified risk factors for cardioembolic ischemic stroke, a common and devastating complication. The study provided initial guidelines for identifying and treating at-risk patients[12].

(1) Rogue AL et al. "Trypanosoma cruzi transmission cycle among wild and domestic mammals in three areas of orally transmitted Chagas disease outbreaks." *Am J Trop Med Hyg.* 2008 Nov; 79(5): 742-9.
(2) Guimarães AC et al. "In silico reconstruction of the amino acid metabolic pathways of Trypanosoma Cruzi." *Genet Mol Res.* 2008 Sept 23; 7(3): 872-82.
(3) Absalon S et al. "Flagellum elongation is required for correct structure, orientation and function of the flagellar pocket in Trypanosoma brucei." *J Cell Sci.* 2008 Nov 15; 121(Pt 22): 3704-16.
(4) Goytia M et al. "Molecular and structural discrimination of proline racemase and hydroxyproline-2-epimerase from nosocomia and bacterial pathogens." *PLoS ONE.* 2007 Sep 12; 2(9): e885.
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(6) Medeiros GA et al. "Treatment of chronically Trypanosoma cruzi-infected mice with a CCR1/CCR5 antagonist (Met-RANTES) results in amelioration of cardiac tissue damage." *Microbes Infect.* 2008 Dec 7. [Epub ahead of print]
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(8) Lorena VM et al. "Cellular immune response from Chagasic patients to CRA or FRA recombinant antigens of Trypanosoma cruzi." *J Clin Lab Anal.* 2008; 22(2): 91-8.
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(10) Abad-Franch F et al. "Ecology, evolution, and the long-term surveillance of vector-borne Chagas disease: A multi-scale appraisal of the tribe Rhodniini (Triatominae)." *Acta Trop.* 2008 Jun 21. [Epub ahead of print]
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(12) De Sousa AS et al. "Prevention strategies of cardioembolic ischemic stroke in Chagas' disease." *Arg Bras Cardiol.* 2008 Nov; 91(5): 306-10.

Schistosomiasis

Schistosomiasis, also known as bilharzia, is a parasitic disease endemic to regions of Africa, Asia, and South America, particularly in areas where water contains numerous freshwater snails. Although it has a low mortality rate, schistosomiasis can become a chronic illness that damages internal organs and impairs growth and cognitive development in children.

IN 2008

- ☐ analysis of the incidence and urogenital effects of co-infection with schistosomiasis and sexually-transmitted infections in Madagascar
- ☐ first systematic study of *S. mansoni* infection in older individuals by Fiocruz in Brazil
- ☐ link between schistosomiasis and anemia in Nigerien schoolchildren
- ☐ proposal of new molecules as targets for the treatment of schistosomiasis by the Institut Pasteur in Lille

EPIDEMIOLOGY

The **Institut Pasteur in Madagascar** compared urogenital ultrasound results from individuals from a high-endemic and a low-endemic village in northern Madagascar. The findings clarified the urogenital pathology of Schistosoma infection, including changes to the seminal vesicles in men[1].

In another study in Madagascar, researchers found that 35% of women and 17% of men infected with *S. haematobium* had concordant sexually transmitted infections[2].

In Brazil, a review of the literature by researchers at **Fiocruz** found a strong association between *Schistosoma* infection and low socio-economic status in both urban and rural settings[3].

DIAGNOSIS, THERAPY, VACCINE

Researchers at the **Institut Pasteur in Lille** proposed new molecules (protein tyrosine kinases) as targets for the treatment for schistosomiasis, as the current treatment (praziquantel) is susceptible to developing resistance[4].

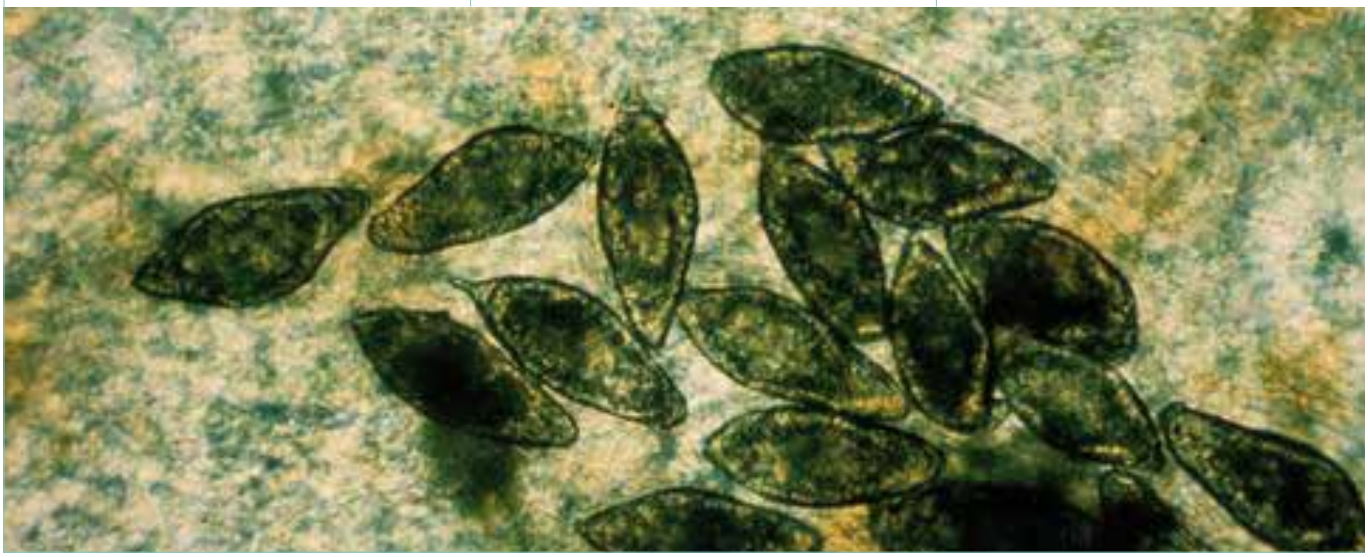
IMMUNOLOGY

Fiocruz undertook the first systematic study of the immune response of older individuals residing in areas endemic for *S. mansoni*[5]. The findings suggest that some individuals are protected, in part due to the development of an innate immune response that compensates for the natural decline in T-cell function that accompanies aging. Other immunology studies undertaken by **Fiocruz** have suggested inflammation and a skewed Th2 immune response as causal mechanisms for neuro-schistosomiasis[6], and a link between eosinophils and fibrosis in *S. mansoni* morbidity.

BASIC RESEARCH

Researchers at the **Institut Pasteur– Cenci Bolognetti Foundation** reported on the crystal structure of a key enzyme expressed by schistosomes that is crucial for the parasite's survival in the host[7].

Eggs of *Schistosoma haematobium* in a human rectal biopsy.
© *Rodhain, F. / Institut Pasteur*



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(6) Ferrari TC et al. "Immune response and pathogenesis of neuroschistosomiasis mansoni." *Acta Trop.* 2008 Nov-Dec; 108(2-3); 83-5.

CLINICAL RESEARCH

The **CERMES** has been designated to evaluate Niger's national control program to reduce morbidity due to schistosmiasis by performing annual mass treatment with praziquantel. Results indicate that one year after treatment, schoolchildren included in the cohort were significantly less likely to be infected, and their hemoglobinemia increased significantly[8].

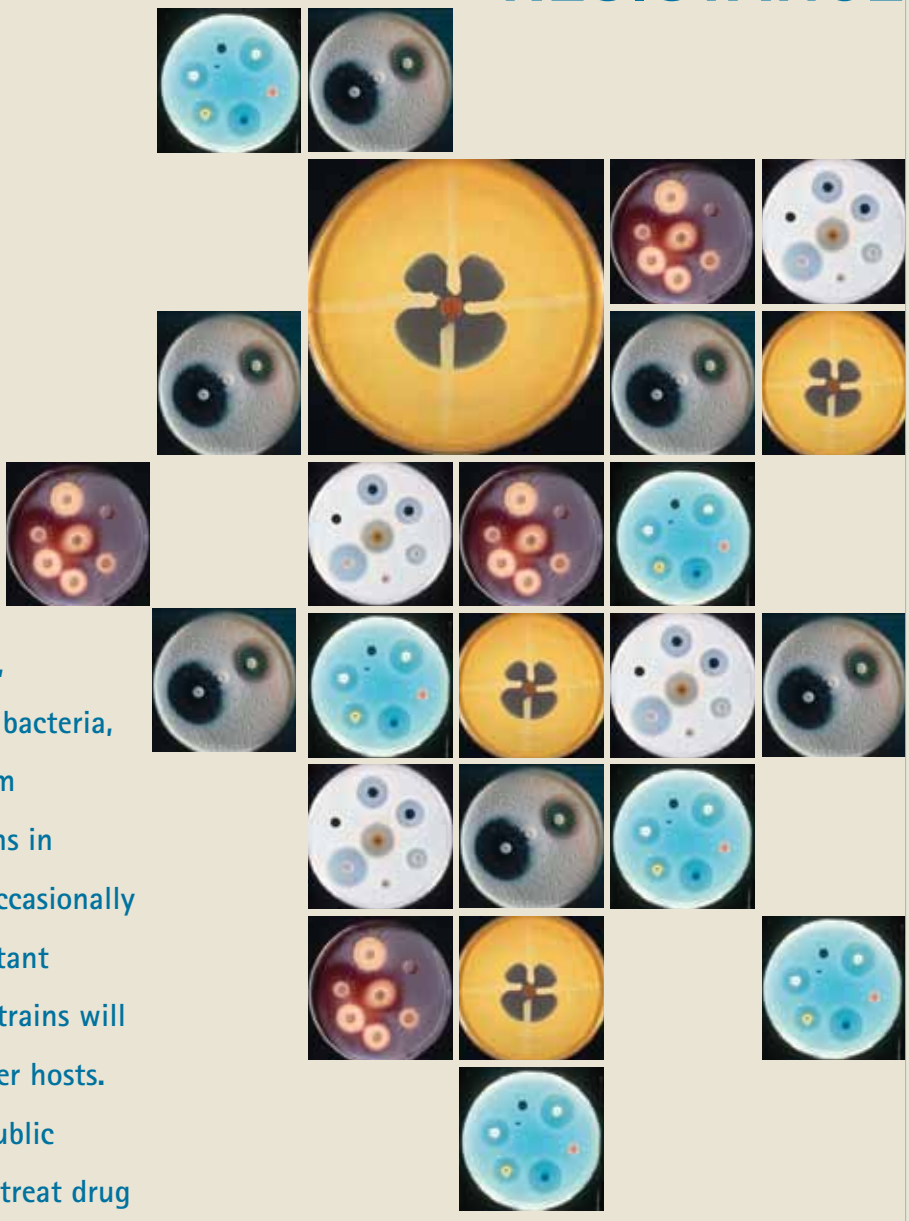
A study performed by the **Institut Pasteur in Madagascar** suggested that *S. haematobium* infection may be linked to decreased sperm quality (sperm apoptosis and a reduced production of seminal fluid)[9].

Institut Pasteur in Côte d'Ivoire

(7) Angelucci F et al. "Glutathione reductase and thioredoxin reductase at the crossroad: the structure of *Schistosoma* mansoni thioredoxin glutathione reductase." *Proteins.* 2008 Aug 15; 72(3): 936-45.
(8) Tohon WB et al. "Controlling schistosomiasis: significant decrease of anaemia prevalence one year after a single dose of praziquantel in Nigerian schoolchildren." *PLoS Negl Trop Dis.* 2008 May 28; 2(5): e241.
(9) Leutscher PD et al. "Semen quality in *Schistosoma* haematobium infected men in Madagascar." *Acta Trop.* 2009 Jan; 109(1): 41-4.

PART 3

MONITORING DRUG RESISTANCE



Resistance to antimicrobial agents, whether designed to fight viruses, bacteria, or parasites, is an everyday problem in public health. Random mutations in pathogens' genetic material will occasionally result in phenotypes that are resistant to antimicrobials, and these new strains will go on to reproduce and infect other hosts. Researchers and practitioners in public health must therefore continually treat drug resistant infections in individual patients, while simultaneously adopting strategies to fight the emergence of resistance in populations.

Resistance to antivirals

Designing antiviral drugs is particularly challenging because viruses use host cells to replicate. Thus, it can be difficult to target the pathogen without harming the host. This may be one of the reasons that antiviral drugs emerged only in the 1960s, and then by a process of trial and error. The emergence of drug resistance in viruses, reducing the effectiveness of the already limited range of antivirals, is thus particularly problematic.

A collaborative project called "Broad spectrum antiviral agent testing" unites the **Institut Pasteur**, including its National Reference Center on Arboviruses, with the **Institut Pasteur in Shanghai** and the **HKU–Pasteur Research Center**. The project evaluates two classes of antivirals (a molecule derived from interferon and an inhibitor of pyrimidines nucleotides synthesis) designed to fight several viruses, either by targeting specific proteins used by pathogens or by boosting the natural defenses of the host.

In a separate project, the **Institut Pasteur in Iran** reported the absence of primary resistance to lamivudine in hepatitis B viruses circulating in the country[1].

Much of the work taking place in the RIIP on antiviral resistance has to do with antiretroviral treatments for HIV/AIDS. The introduction of such treatments in developing countries has necessitated the creation of surveillance networks for resistant strains, similar to those already functioning in the developed world.

As a result, numerous institutes in the RIIP have embarked upon surveillance activities of this sort. A multi-center project supported by the French Ministry of Foreign Affairs (FSP/RAI/ARV) allowed for the standardization of genetic tests used for studying HIV resistance to ARVs at the **Instituts Pasteur in Algeria, Morocco, Madagascar, Bangui, Ho Chi Minh City**, and **Cambodia**, as well as the **Pasteur Center in Cameroon**. As part of this effort, the Institut Pasteur in Algeria published a study demonstrating the first cases of HIV-1 resistant to all classes of ARVs available in the country (NRTIs, NNRTIs, PIs)[2].

Furthermore, a project financed by the ANRS called "Resistance in the South" has been functioning since 2005 in seven countries (Cambodia, Vietnam, Thailand, Burkina Faso, Cameroon, Côte d'Ivoire, and Senegal), including several member institutes of the RIIP.

Institut Pasteur in Cambodia.

(1) Amini-Bavil-Olyaee S et al. "Hepatitis B virus (HBV) genotype and TMDD motif mutation profile among patients infected with HBV and untreated with lamivudine." *Int J Infect Dis.* 2008 Jan; 12(1): 83-7.
(2) Bouzeghoub S et al. "First observation of HIV type 1 drug resistance mutations in Algeria." *AIDS Res Hum Retroviruses.* 2008 Nov; 24(11): 1467-73.

Resistance to antimalarials

Several families of drugs are used to treat malaria, virtually all of which are subject to resistance by some strains of Plasmodium, *including the most dangerous,* P. falciparum. *Researchers were reminded of the continual need for new drugs to fight the disease in January 2009, when they identified resistance to the first-line drug artesiminin, a treatment whose many years of efficacy may be coming to an end.*

At the forefront of such research is an collaborative project linking researchers at the **Instituts Pasteur in Madagascar** and **Cambodia** and the **CERMES** in Niger, who use molecular markers (pfmdr1 and pfatp6) to study *P. falciparum* resistance to artemisinin derivatives in these three countries. As part of this project, the **Institut Pasteur in Cambodia** conducted a study on resistance to two treatments – artesunate-mefloquine and artemether-lumefantrine – in patients with malaria on the Thai-Cambodian border[1]. The number of copies of the pfmdr1 gene in the *P. falciparum* genome was linked to resistance to the former regime, but not the latter, suggesting a role for other molecular factors.

Conversely, a study in south-eastern Iran conducted by the **Institut Pasteur in Iran** concluded that the pfmdr1 allele was not associated with resistance to chloroquine, whereas the pfcrt allele was[2].

The **Institut Pasteur in French Guiana** is home to a National Reference Center for Malaria Chemoresistance, where researchers perform malaria surveillance, epidemiological studies, and chemoresistance studies for *P. falciparum* in the greater Antilles. One recent study examined resistance to eight anti-malarials in over 1,000 clinical isolates collected from 1994 to 2005, and documented trends such as decreasing susceptibility to mefloquine and, more surpisingly, to dihydroartemisimin[3].

Researchers at the **Institut Pasteur in Côte d'Ivoire** examined clinical isolates of *P. falciparum* for resistance to three anti-malarial drugs (chloroquine, quinine, and artesunate) and found resistance rates of 26.1%, 0%, and 9.5%, respectively[4].

The **Institut Pasteur in Madagascar** conducted a multi-site randomized clinical trial to assess the efficacy of four anti-malarial therapies recommended by the Malagasy national malaria program[5]. For the 1,347 children enrolled, all treatment regimens resulted in clinical cure rates above 96.7% (except for chloroquine), showing relatively low rates of drug resistance compared to other countries in the Indian Ocean region. In another study, researchers evaluated a fluorescence-based assay for testing drug susceptibility in *P. falciparum*, and determined that it was simple, rapid, easy to use, and reliable[6].

Rapid test for malaria, Institut Pasteur in Madagascar.

In Niger, the **CERMES** evaluated the national surveillance network for malaria treatment resistance, which is based on blood finger-pricks on blotting paper. The results showed a homogenous distribution of two mutations conferring resistance and validated this simple method for collecting and testing blood samples[7].

The **Institut Pasteur in Dakar** studied the development of resistance following chemoprophylaxis by comparing polymorphisms in parasite specimens from matched placental and venous blood samples[8]. The results showed that diverse parasite populations can accumulate in the placenta despite chloroquine prophylaxis.

The Antimalarial Resistance Observatory, a network which includes several RIIP institutes, works to identify and fight the emergence of resistant strains in Africa, Asia, and South America. www.oranet.fr

(1) Lim P et al. "Pfmdr1 copy number and arteminisin derivatives combination therapy failure in falciparum malaria in Cambodia." *Malar J.* 2009 Jan 12; 8:11.
(2) Zakeri S et al. "Association of pfcrt but not pfmdr1 alleles with chloroquine resistance in Iranian isolates of *Plasmodium* falciparum." *Am J Trop Med Hyg.* 2008 Apr; 78(4): 633-40.
(3) Legrand et al. "In vitro monitoring of *Plasmodium* falciparum drug resistance in French Guiana: a synopsis of continuous assessment from 1994 to 2005." *Antimicrob Agents Chemother.* 2008 Jan; 52(1): 288-98.
(4) Touré AO et al. "[In vitro susceptibility of *P. falciparum* isolates from Abidjan (Côte d'Ivoire) to quinine, artesunate and chloroquine.]" *Sante.* 2008 Jan-Mar; 18(1): 43-7.
(5) Ménard D et al. "Assessment of the efficacy of antimalarial drugs recommended by the National Malaria Control Programme in Madagascar: up-dated baseline data from randomized and multi-site clinical trials." *Malar J.* 2008 Apr 4; 7:55.
(6) Rason MA et al. "Performance and reliability of the SYBR Green I based assay for the routine monitoring of susceptibility of *Plasmodium* falciparum clinical isolates." *Trans R Soc Trop Med Hyg.* 2008 Apr; 102(4): 346-51.
(7) Ibrahim ML et al. "[*Plasmodium* falciparum chlorquine and pyrimethamine resistance monitoring network with molecular tools in the Niger River valley, Republic of Niger.]" *Bull Soc Pathol Exot.* 2008 Feb; 101(1): 47-9.
(8) Niang M et al. "Accumulation of CVIET Pfcrt allele of *Plasmodium* falciparum in placenta of pregnant women living in an urban area of Dakar, Senegal." *J Antimicrob Chemother.* 2008 Nov; 62(5): 921-8.

Resistance to antibiotics

Bacteria may be particularly able to develop resistance to drugs designed to fight them due to the horizontal exchange of plasmids containing genetic material. The Institut Pasteur studies such developments in its National Reference Center for Resistance to Antibiotics, which catalogues bacterial "reference strains," performs in vitro *evaluations of the efficacy of new drugs, and studies bacterial resistance mechanisms. Within the RIIP, a large number of studies are currently underway to track this significant threat to public health.*

STUDY FINDINGS	INSTITUTE INVOLVED	BIBLIOGRAPHIC REFERENCE
Tuberculosis		
A study on the molecular basis of drug resistance in tuberculosis strains circulating in Bulgaria found 28% prevalence of resistant strains among newly-diagnosed patients.	Stephen Angeloff Institute	Valcheva V et al. "Molecular snapshot of drug-resistant and drug-susceptible Mycobacterium tuberculosis strains circulating in Bulgaria." *Infect Genet Evol.* 2008 Sept; 8 (5): 657-63.
The high levels of polymorphisms in DNA repair, recombination, and replication genes for tuberculosis may serve as a starting point for resistance.	Institut Pasteur	Dos Vultos T et al. "Evolution and diversity of clonal bacteria: the paradigm of Mycobacterium tuberculosis." *PLoS ONE.* 2008 Feb 6; 3 (2): e1538.
A molecular characterization of ofloxacin-resistant strains suggests that the spread of multi-drug resistant tuberculosis in Russia is due in part to the prevalence of the Beijing genotype.	Institut Pasteur in Saint Petersburg	Mokrousov I et al. "Molecular characterization of ofloxacin-resistant Mycobacterium tuberculosis strains from Russia." *Antimicrob Agents Chemother.* 2008 Aug; 52 (8): 2937-9.
A study evaluating the resazurin microtitre assay determined that it is sensitive and specific enough to detect strains of tuberculosis that are resistant to isoniazid and rifampicin.	Institut Pasteur in Madagascar	Rivoire N et al. "Evaluation of the resazurin assay for the detection of multidrug-resistant Mycobacterium tuberculosis in Madagascar." *Int J Tuberc Lung Dis.* 2007 Jun; 11 (6): 683-8.
Multidrug-resistant strains of *Mycobacterium tuberculosis* in Bangui might have emerged from a single multidrug resistant family.	Institut Pasteur in Bangui	Nouvel LX et al. "Multidrug-resistant Mycobacterium tuberculosis, Bangui, Central African Republic." *Emerg Infect Dis.* 2006 Sept; 12 (9): 1454-6.
A study on an HIV-positive population in New York City followed the evolution of drug resistance in *M. tuberculosis* and described genotypic and phenotypic characteristics of multidrug-resistant strains.	Scientific Institute of Public Health, Belgium	Bifani P et al. "The evolution of drug-resistance in Mycobacterium tuberculosis: From a mono-rifampicin resistant cluster into increasingly multidrug resistant variants in an HIV sero-positive population." *J Infect Dis.* 2008 Jul 1; 198(1): 90-4.
Cholera		
All strains identified during an outbreak in Cameroon in 2004-2005 were shown to be multidrug-resistant, but all were still susceptible to tetracycline, recommended by the WHO for treating cholera in adults.	Pasteur Center in Cameroon	Ngandijo A et al. "Antimicrobial resistance and molecular characterization of Vibrio cholerae O1 during the 2004 and 2005 outbreak of cholera in Cameroon." *Foodborne Pathog Dis.* 2008 Nov 9. [Epub ahead of print].
Isolates collected during several cholera outbreaks in Iran in 2005 showed the strains to be highly homogenous, revealing the dissemination of a single *V. cholerae* strain in Iran in 2005.	Institut Pasteur in Iran	Pourshafie MR et al. "Dissemination of a single Vibrio cholerae clone in cholera outbreaks during 2005 in Iran." *J Med Microbiol.* 2007 Dec; 56 (Pt 12): 1615-9.
Plague		
The first multidrug resistant strain of *Y. pestis* owes its resistance to a self-transmissible plasmid that appears to originate in multidrug-resistant zoonotic pathogens associated with agriculture in the United States. Multidrug-resistant plague represents a significant public health danger and bio-defense threat.	Institut Pasteur	Welch TJ et al. "Multiple antimicrobial resistance in plague: an emerging public health risk." *PLoS ONE.* 2007 Mar 21; 2 (3): e309.
Bacterial meningitis		
New results on the etiology of meningitis – and resistance profiles of potential pathologies causing it – suggest that the probabilistic treatment with ampicillin and chloramphenicol for children with meningitis must be reconsidered.	Institut Pasteur in Bangui	Bercion R et al. "Acute bacterial meningitis at the 'Complexe Pédiatrique'of Bangui, Central African Republic.'" *J Trop Pediatr.* 2008 Apr; 54 (2): 125-8.

STUDY FINDINGS	INSTITUTE INVOLVED	BIBLIOGRAPHIC REFERENCE
Diarrheal diseases		
Strains of *E. coli* demonstrating high incidence of resistance to tetracycline (63%), ampicillin (62%), and other antibiotics (though not quinolones), are an important causative agent of diarrhea in Iran.	Institut Pasteur in Iran	Aslani MM et al. "Molecular detection and antimicrobial resistance of diarrheagenic Escherichia coli strains isolated from diarrheal cases." *Saudi Med J.* 2008 Mar; 29 (3): 388-92.
A prospective study in four urban health centers of Shigella strains causing invasive diarrhea in Bangui, CAR showed that multidrug-resistance was common (e.g. to amoxicillin, sulphamethoxazole-trimethoprim and chloramphenicol). No strains were resistant to quinolone and fluoroquinolones.	Institut Pasteur in Bangui	Bercion R et al. "Distribution and antibiotic susceptibility of Shigella isolates in Bangui, Central African Republic." *Trop Med Int Health.* 2008 Apr; 13 (4): 468-71.
A study on the prevalence of genes encoding for beta-lactamase, an enzyme that deactivates certain antibiotics, in enterobacteria circulating in Abidjan showed 97.6% resistance to cotrimoxazole, and high rates for other antibiotics too.	Institut Pasteur in Côte d'Ivoire	Guessennd N et al. "[Qnr-type quinolone resistance in extended-spectrum beta-lactamase producing enterobacteria in Abidjan, Ivory Coast.]" *Pathol Biol (Paris). 2008 Nov-Dec; 56 (7-8): 439-46.*
Researchers reported that multi-drug resistant *Salmonella enterica* (Newport serotype) has caused sporadic cases and outbreaks in France in 2000-2005. The strain was mostly likely introduced through imported food products.	Institut Pasteur	Egorova S et al. "Ceftriaxone-resistant salmonella enterica serotype Newport, France." *Emerging Infect Dis.* 2008 Jun; 14(6): 954-7.
Molecular characterization of a genomic island in *Samonella enterica* (serovar Kentucky) revealed that the region undergoes sequence- and transposon-mediated genetic rearrangements, resulting in a higher diversity of multi-drug resistant phenotypes.	Institut Pasteur	Doublet B et al. "Novel insertion sequence- and transposon-mediated genetic rearrangements in genomic island SGI1 of Samlonella enterica serovar Kentucky." *Antimicrob Agents Chemother.* 2008 Oct; 52(10): 3745-54.
Staphylococci		
A cross-country study (Algeria, Mali, Moldova, and Cambodia) on mutations in the staphylococcus chromosome that confers methicillin resistance showed it to be widespread and highly diversified.	Institut Pasteur in Cambodia	Ruppé E et al. "Diversity of SCCmec structures in Methicillin – Resistant Staphylococcus epidermidis and Staphylococcus haemolyticus among outpatients from four countries." *Antimicrob Agents Chemother.* 2009 Feb; 53 (2): 442-9.
Researchers tested naturally occurring antimicrobial peptides derived from amphibian skin against multidrug-resistant strains of common nosocomial infections, including *Staphylococcus aureus*. All 5 peptides were bactericidal against all bacterial species tested, and 1 peptide was particularly effective in the presence of human serum.	Institut Pasteur – Cenci Bolognetti Foundation	Mangoni ML et al. "Comparative analysis of the bactericidal activities of amphibian peptide analogues against multidrug-resistant nosocomial bacterial strains." *Antimicrob Agents Chemother.* 2008 Jan; 52 (1): 85-91.
A study of 574 clinical isolates of *S. aureus*, tested against 18 antibiotics. Methicillin resistance was found in 6.5% of community-acquired strains and in 4.4% of nosocomial infections, which is still rather low. This was the first study of its kind in Madagascar.	Institut Pasteur in Madagascar	Randrianirina F et al. "In vitro activities of 18 antimicrobial agents against Staphylococcus aureus isolates from the Institut Pasteur of Madagascar." *Ann Clin Microbiol Antimicrob Chemother.* 2007 May 23rd; 59 (2): 309-12.
Neisseria gonorrhea		
Researchers investigated strains isolated in Bangui, Yaoundé, and Antananarivo, as well as Ho Chi Minh City and Nha Trang in Vietnam. Patterns of resistance were similar in the African cities (for example, ciprofloxacin remained highly effective), but differed from the Vietnamese samples, reinforcing the need for local/regional guidelines.	Instituts Pasteur in Ho Chi, Nha Trang, New Caledonia, Bangui, and Madagascar; the Pasteur Center in Cameroon	Cao V et al. "Antimicrobial susceptibility of Neisseria gonorrhoeae strains isolated in 2004-2006 in Bangui, Central African Republic, Yaoundé, Cameroon; Antananarivo, Madagascar; and Ho Chi Minh Ville and Nha Trang, Vietnam." *Sex Transm Dis.* 2008 Nov; 35 (11): 941-5.
The Institut Pasteur in New Caledonia developed two new real-time PCR assays capable of identifying strains that are still susceptible to penicillin. This research emerged as part of a project with the Instituts Pasteur in Madagascar and Nha Trang. The project follows mutations in two genes (ponA and penA) in *N. gonorrhoeae* and *N. meningitidis* that are associated with reduced susceptibility to penicillin.	Institut Pasteur in New Caledonia	Vernel-Pauillac F et al. "Genotyping as a tool for antibiotic resistance surveillance of Neisseria gonorrhoeae in New Caledonia: evidence of a novel genotype associated with reduced penicillin susceptibility." *Antimicrob Agents Chemother.* 2008 Sep; 52 (9): 3293-300.

PART 4
TECHNICAL PLATFORMS

BIO-SAFETY LEVEL 3 FACILITIES IN THE RIIP

BSL-3 LABORATORIES

- Abidjan (Côte d'Ivoire)
- Antananarivo (Madagascar)
- Athens (Greece)
- Brussels (Belgium)
- Casablanca (Morocco)
- Cayenne (French Guiana)
- Hanoi (Vietnam)
- Lille (France)
- Paris (France)
- Phnom Penh (Cambodia)
- Seoul (South Korea)
- Tehran (Iran)
- Yaounde (Cameroon)

BSL-3 LABORATORIES (under construction)

- Alger (Algeria)
- Bangui (Central African Republic)
- Bucarest (Romania)
- Dakar (Senegal)
- Hong Kong (China)
- Laval (Canada)
- Shanghai (China)

Inauguration of the BSL-3 laboratory (avian flu module) at the Institut Pasteur in Cambodia, April 25, 2008. From left to right: French Assistant Secretary of State Rama Yade, Cambodian Minister of Health Dr. Mam Bunheng, Director of the Institut Pasteur in Cambodia Prof. Jean-Louis Sarthou, and Director of International Affairs at the Institut Pasteur Dr. Yves Charpak.

OTHER CORE FACILITIES

CERMES
- Production and evaluation of immunochromatographic assays

HKU-PASTEUR RESEARCH CENTER
- Flow cytometry services (FACSCalibur, LSR II)

INSTITUT ARMAND FRAPPIER
- Confocal microscopy and digital imaging
- Electron microscopy
- Experimental biology center
- Flow cytometry
- Mass spectrometry
- Proteomic analysis

INSTITUT PASTEUR
Proteomics and interactomics
- Protein production
- Biophysics of macromolecules and interactions
- Proteomics
- Peptide sequencing
- Crystallography

Comparative and functional genomics
- DNA and genomic sequencing
- Oligonucleotide synthesis
- Micro-arrays
- Genotyping of pathogens and public health

Cellular and molecular imaging
- Dynamic imaging
- Cytometry
- Electronic microscopy
- Cryomicroscopy

Bioinformatics and databases
- Software and databases
- Genomic annotation and databases

Zoopole
- Central animal facility
- Mouse transgenesis
- *Anopheles* production and infection with *P. falciparum*

Collections
- Bacterial collection
- Fungal collection
- Cyanobacteria

INSTITUT PASTEUR IN CAMBODIA
- BLS-3 animal facility
- Flow Cytometry (FACSCalibur)

INSTITUT PASTEUR-FONDATION CENCI BOLOGNETTI
- Transcriptomics
- Bioinformatics

INSTITUT PASTEUR IN GREECE
- Transgenics
- Imaging
- Microarrays

INSTITUT PASTEUR IN KOREA
- Cell biophysics
- Diagnostics with microfluidics technology
- Discovery cell biology
- Dynamic imaging platform with ultra high-speed multi-D imaging
- Image mining
- Screening technology and pharmacology with automated confocal microscopy

INSTITUT PASTEUR IN LILLE
- Transcriptomics
- Genomics
- BLS-3 animal facility
- Bioinformatics
- Microarrays

INSTITUT PASTEUR IN MADAGASCAR
- Production and evaluation of immunochromatographic assays

INSTITUT PASTEUR IN MONTEVIDEO
- Transgenic and experimental animals unit
- Bioinformatics unit
- Protein crystallography, biophysics, and production
- Analytic biochemistry and proteomics

INSTITUT PASTEUR IN SHANGHAI - CHINESE ACADEMY OF SCIENCES
- Scientific and viromic imaging (proteomics and genomics)
- Micro-injection in frog oocytes
- Imaging (laser scanning confocal microscope, fluorescent inverted microscope, phosphoImager)
- BSL-2 + laboratory, including animal facilities
- Recombinant protein production (baculovirus, S_2 drosophila cells, yeast) and purification (FPLC)

SCIENTIFIC INSTITUTE OF PUBLIC HEALTH, BELGIUM
- Fungal collection BCCM/IHEM

PART 5
INTERNATIONAL TRAINING

Each year, the RIIP organizes courses and workshops open to the personnel of member institutes as well as to external researchers, technicians, or students who will use acquired knowledge and techniques in other national or regional structures.

Thus, in 2008, 16 courses on various scientific topics were organized in 11 different countries, including five in Africa, seven in Asia, three in Latin in America, and one in the Middle East.

Institut Pasteur in Laos

LOCATION	DATE	COURSE
Institut Pasteur in Cambodia	February 13-15, 2008	Regional Workshop on Biosafety Levels 2/3 (in French)
HKU-Pasteur Research Center	February 15, 2008	Cell Imaging Workshop
Institut Pasteur in Iran	March 1-7, 2008	Leishmania: developmental biology, leishmaniasis, treatment and vaccine development
Institut Pasteur in Madagascar	March 10 – April 18, 2008	Malaria Workshop, 6th edition (in French)
Regional Institute for Public Health, Benin	March 31 – April 26, 2008	International Course on Epidemiology and Applied Computing (in French)
Harmanus Cape Town, South Africa	March 1-9, 2008	Molecular and Cellular Basis of Infection
Institut Pasteur in Côte d'Ivoire	April 14-25, 2008	Regional Course on Antibiograms, Level 1: Antibiograms and the proper use of antiobitics in West Africa (in French)
Shanghai CDC, China	May 12-22, 2008	Tuberculosis: from genetics to molecular diagnosis and drug susceptibility testing
Capital Medical University, Beijing, China	June 1-10, 2008	Second Asian Workshop on Genomics and Community Genetics
Shanghai Life Science Information Center, Shanghai, China	June 12-14, 2008	Third Forum AREVA-Pasteur on Mosquito and Tick-Borne Viruses
Universidade Federal de Santa Catarina, Florianopolis, Brazil	June 30 – July 12, 2008	Advanced Course on Bioinformatics and Comparative Genome Analysis
Institut Pasteur in Cambodia	2008	Second Seminar on Human Rabies Prophylaxis in Cambodia: Follow-up after 5 years (in French)
Institut Pasteur in Madagascar	2008	Follow-up seminar on the new organization of Anti-Rabies centers in Madagascar inplemented in 2007 (in French)
HKU-Pasteur Research Center	July 7-25, 2008	5th Pasteur-Asia Virology Course: Viruses and cancer, Influenza
Aguascalientes, Mexico	August 25 – September 5, 2008	International Course on Innate Immunity against Pathogens (in Spanish)
Institut Pasteur in Saint Petersburg	September 16-18, 2008	Surveillance of vaccine-preventable infections (pertussis, diptheria) as of the present (in French)
HKU-Pasteur Research Center	October 23 – November 5, 2008	First Pasteur-Asia Immunology course
Institut Pasteur in Montevideo	November 2008	Genetics of Laboratory Rodents

PARTNERS

The RIIP and its member institutes are recognized as essential partners in international public health and biomedical research. The Institut Pasteur alone counts over 1,000 international collaborations, with many more in the RIIP, covering all areas of research, training, and public health activities. Some of our partners include:

INTERNATIONAL ORGANIZATIONS

- World Health Organization
- European Commission (EC)
- European & Developing Countries Clinical Trials Partnership
- Global Alliance for Vaccines and Immunization (GAVI)
- Amsud-Pasteur collaboration, including 51 partners within Latin America
- United Nations Educational, Scientific, and Cultural Organization (UNESCO)
- United Nations Children's Emergency Fund (Unicef)
- International Vaccine Institute
- European Center for Disease Prevention and Control

BILATERAL INITIATIVES

- French Agency for Development
- ESTHER (French Network for Therapeutic Solidarity in Hospitals)
- American Centers for Disease Control (CDC), Department of Health and Social Services (DHSS), and the U.S. Agency for International Development, National Institutes of Health (NIH)
- Max Planck Institute
- French Ministries of Foreign Affairs (MAE), Higher Education and Research (MESR), Health, and National Education
- Union for the Mediterranean
- Mexican National Council for Science and Technology (CONACYT)
- RIKEN and NIID in Japan
- Numerous French national research agencies: AIRD, ANRS, CEA, CIRAD, CNES, CNRS, IFREMER, INRA, INRIA, INSERM, InVS, IRD, IRES...
- Weizmann Institute of Science

FOUNDATIONS, ASSOCIATIONS, AND UNIVERSITIES

- Bill and Melinda Gates Foundation
- Drugs for Neglected Diseases Initiative (DNDi)
- Multilateral Initiative on Malaria (MIM)
- Friends of the Global Fund
- Rockefeller Foundation
- Medical Research Council
- Wellcome Trust
- Fondation Mérieux
- Harvard School of Public Health
- Qatar Foundation
- International Association of National Public Health Institutes
- French Association for Preventive Medicine (AMP)
- Doctors without Borders (MSF)
- Francophone University Agency (AUF)
- French Red Cross (CRF)
- Médecins du Monde (MDM)
- Li Ka-Shing Foundation
- London School of Hygiene and Tropical Medecine
- Imperial College of London
- Foundation for Innovative New Diagnostics (FIND)
- Fondation Pierre Ledoux Jeunesse Internationale

PRIVATE SECTOR

- Areva
- Astra Zeneca
- Bio Mérieux
- BioRad
- BNP Paribas
- EDF
- Ethypharm
- GlaxoSmithKline (GSK)
- NATIXIS
- Pierre Fabre Santé
- Roche
- Sanofi Aventis
- Sanofi-Pasteur
- SEPPIC-Air Liquide
- Total
- Veolia

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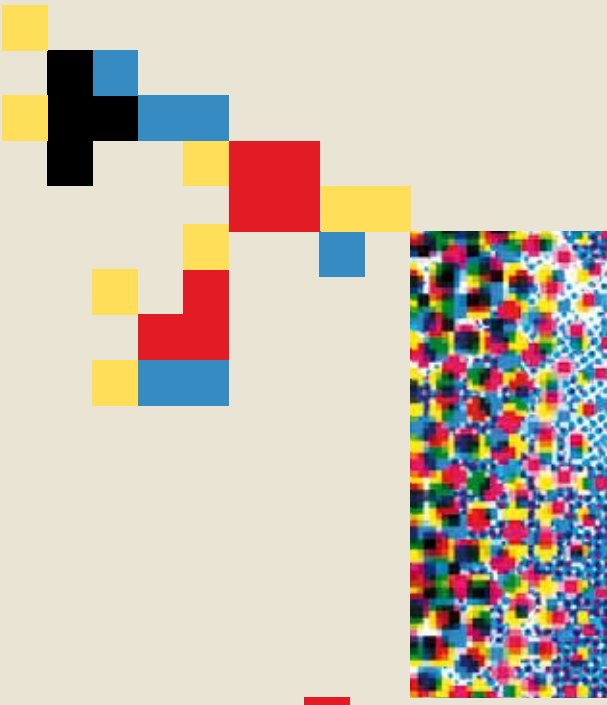

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