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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)
EPI 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 Health (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
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.

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.

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.

I would like to offer special thanks to Sarah Dalglish for her tenacity and thoroughness, with help from Eliane Coeffier 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.
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.”
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)

Institut Pasteur in Cambodia (established in 1995)

Institut Pasteur in Korea (established in 2003)

Institut Pasteur in New Caledonia (established in 1955)

Institut Pasteur in Laos (established in 2007)

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

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

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

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

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.

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 travelers 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 activities 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.

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.

A number of RIIP member institutes are also involved in the production of 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

The Institut 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.

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The rabies vaccine is available at the Pasteur Center in Cameroon and at the Pasteur Center 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 immunoglobulins.

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

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- occupational and school health
- vector control
- health education
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

<table>
<thead>
<tr>
<th>INSTITUTE</th>
<th>WHO COLLABORATING CENTERS</th>
<th>NATIONAL REFERENCE CENTERS RECOGNIZED BY WHO</th>
<th>REGIONAL REFERENCE LABORATORIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institut Pasteur in Cambodia</td>
<td>Flu. Emerging infectious diseases, SARS. Arboviruses. Rabies</td>
<td>Avian flu (WHO). Malaria rapid diagnostic test (WHO)</td>
<td></td>
</tr>
<tr>
<td>Cantacuzino Institute (Romania) †</td>
<td>Flu</td>
<td>Flu. Poliomyelitis. Measles/rubella</td>
<td>Flu (WHO)</td>
</tr>
<tr>
<td>Institut Pasteur in Côte d’Ivoire</td>
<td>Arboviruses and hemorrhagic fevers</td>
<td>Flu. Poliovirus. Measles</td>
<td>Avian flu (WHO)</td>
</tr>
<tr>
<td>Institut Pasteur in Dakar</td>
<td>Avian flu (WHO)</td>
<td>Avian flu (WHO)</td>
<td></td>
</tr>
<tr>
<td>Pasteur Center in Cameroon</td>
<td>Occupational health</td>
<td>Flu. Poliomyelitis</td>
<td>Avian flu (WHO)</td>
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<tr>
<td>NIHE (Vietnam)</td>
<td>Arboviruses and Influenzae viruses.* Malaria chemoresistance*</td>
<td>Leishmaniasis. Neisseria gonorrhoeae</td>
<td></td>
</tr>
<tr>
<td>Institut Pasteur in French Guiana</td>
<td>Arboviruses and Influenzae viruses.* Malaria chemoresistance*</td>
<td>Leishmaniasis. Neisseria gonorrhoeae</td>
<td></td>
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<td>Institut Pasteur in Greece</td>
<td>Flu. Poliomyelitis. Measles/rubella. Flu (WHO)</td>
<td>Avian flu (WHO)</td>
<td></td>
</tr>
<tr>
<td>Institut Pasteur in Iran</td>
<td>Rabies</td>
<td>Arboviruses and hemorrhagic fevers</td>
<td>Avian flu (WHO)</td>
</tr>
<tr>
<td>Institut Pasteur in Madagascar</td>
<td>Plague</td>
<td>Flu. Avian flu. Poliomyelitis. Measles</td>
<td>Avian flu (WHO)</td>
</tr>
<tr>
<td>Institut Pasteur in New Caledonia</td>
<td>Flu</td>
<td>Regional observatory for pneumococcus</td>
<td></td>
</tr>
<tr>
<td>Institut Pasteur in Tunis</td>
<td>Leishmaniasis</td>
<td>Poliovirus (WHO)</td>
<td>Poliovirus. Measles. Papillomavirus</td>
</tr>
</tbody>
</table>

* 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
- Toxicogenic 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

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

**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)**

(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.


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® and integrase inhibitors(8).

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(9). The Institut Pasteur in Korea is using a high-volume screening platform to identify medications with identical targets.

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 “Pedicam” 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(10).

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.

[References]

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).

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.(2) Finally, they evaluated the performance of four HBV diagnostic kits.(2)

Researchers at the Institut Pasteur in Morocco demonstrated the predominance of the HBV genotype D in that country.(3) 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.(4)

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.(5)

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.

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 the 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.(6)

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.

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

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[12]
- apparent proof of intra-familial transmission of HCV[12]

**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.

**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.

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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\(^9\). In the Molecular Genetics of Respiratory Viruses unit, researchers identified cellular and viral factors that limit replication of type A influenza viruses in humans\(^1\).

Finally, the HKU-Pasteur Research Center has identified cellular 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 an 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:

  - 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.

  - 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).

  - 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.

  - 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 (Romainia), the Stephan Angeloff Institute (Bulgaria), and the Instituts Pasteur in Cambodia, Shanghai and Lille.


\(^{11}\) 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].

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.

Mosquito nets protect against 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.

**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.

Denframe: Improving dengue diagnosis

The Denframe project, financed by the European Union, unites 13 laboratories including five institutes in the RIIP: the Institut 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.
- 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.

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.

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 biocology 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.

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

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

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 RIIIP 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].

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.

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.

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

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.

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.

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. 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.

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.

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.

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).

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 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(12). Another study identified the potential role of adenovirus vectors in the development of an oral rabies vaccine for dogs(13).

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

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

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

**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 Institut Pasteur in Saint Petersburg and Dakar, the Cantacuzino Institute (Romania), and the Institut Pasteur have created the project “Circulation of polioviruses and non-polio enteroviruses in the environment.” This project is assessing the risk of re-emergence of recombinant strains in waste water.

**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. 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.

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

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. Finally, the Institut Pasteur in Greece reported a rare type of recombination in an oral vaccine-derived poliovirus.

**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

**BASIC RESEARCH**
Researchers from the Institut Pasteur proved the link between the pathogenicity of recombinant polioviruses and type C enteroviruses.

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**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.

**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.

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.

**GENETIC AND MOLECULAR STUDIES**

The NIHE in Hanoi is directing the BASE project (Bac giang Acute Syndrome of Encephalitis) in collaboration with the Laboratoire 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 Institut 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.

**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 Flavi-virus-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.

**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.

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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 Virology 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 workshop on the detection of human papillomaviruses[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 Vanuatu 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].

Papillomavirus. Causes a proliferation of the epithelium leading to growths that are usually benign and sometimes cancerous. Colorized image. © Orth, G.; Croissant, O. / Institut Pasteur

Tuberculosis is an airborne bacterial infection, 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.

**SURVEILLANCE AND PUBLIC HEALTH**

The Institut 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.

**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 homogeneous 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 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.molecurartb.org

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human host cells (macrophages and dendritic cells), demonstrating an "extraordinary plasticity" of host and pathogen responses to infection[9]. The same team analyzed the DNA repair, recombination and replication (3R) genes of \textit{M. tuberculosis} using bioinformatics, yielding unexpectedly high levels of polymorphisms driven by this family[10].

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[11].

Researchers from the Institut Pasteur in Lille reported on a three-year population-based study of \textit{M. tuberculosis} strains, reinforcing the use of the MIRU-VNTR technique in epidemiological and phylogenetic screening[12].

The Institut Pasteur in Tunis developed a microarray targeting nearly all of the PE/PPE multigene families of \textit{M. tuberculosis}. Researchers used this microarray to detect significant levels of homologous recombination, which may have important implications regarding pathogenicity[13].

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 \textit{M. tuberculosis} strains of the W-Beijing family, its differential virulence, and host immune responses.

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 \textit{Pneumocystis jiroveci pneumonia} and pulmonary tuberculosis[14].

\textbf{CO-INFECTION}

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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 RILP member institutes are seeking new tools to fight the disease via extensive field and laboratory research.

**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.

**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].

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(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.
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.

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 vibrios 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 vibrios 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].

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

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.

**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).

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.

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 meningococci, 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[1].

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[2]. 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[3].

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[4].

Researchers at 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).

References:
Diarrhoeal diseases

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

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

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 dysenteriae type 1. This study, a collaboration between field physicians and microbiologists, will serve as the basis for monitoring the disease over the long term.

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. Another study evaluated the WHO’s Salmonella Surveillance 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.

EPIDEMIOLOGY

The Institut Pasteur in Iran identified the STEC and EPEC strains of E. coli as the most important causative agents of diarrhoea in Iran. Another study determined that toxicity and antibiotic resistance are the main contributing factors to the virulence of Iranian isolates of E. coli. 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. The Institut Pasteur in Côte d’Ivoire detected by RT-PCR the first cases of astrovirus in human diarrhoeal stools in Abidjan. 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

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

**GENETIC AND MOLECULAR STUDIES**

Researchers in the Laboratory for Enteric Bacterial Pathogens at the Institut Pasteur published an article on the phylogenetic 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.

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

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 underlying the danger of cryptosporidiosis, a potentially fatal diarrheal infection, for immuno-compromised patients. 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.

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.

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**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.

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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.

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).

Researchers at the Institut Pasteur also reported, for the first time, a protein called Loa22 that is essential to the virulence of Leptospira interrogans(5).

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
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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)(6).

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

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.

EPIEMIOLOGY

A project bringing together the Institut 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 cytokinin-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 Institut 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(2).

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(3). Another study confirmed, via genotyping and serology analysis, that the majority of Iranian strains of H. pylori are positive for the cagA gene(4).

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(5).

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(6).

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(7).

Another team at the Institut Pasteur developed systems to engineer conditional mutants of essential genes of H. pylori(8). 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(9). Other studies highlighted the importance of channel-mediated potassium uptake(10) and genes coding for carbonic anhydrases(11) in H. pylori for efficient gastric colonization.

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

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/

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 \textit{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 \textit{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.

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

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.

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.

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.

ENTOMOLOGY
The Institut Pasteur – Cenci Bolognetti Foundation developed a new approach to analyzing genetic differentiation within Anopheles gambiae subspecies. 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.

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.

In collaboration between the CERMES in Niger and the Institut 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. Another study determined upper and lower limits for the concentration of Plasmodium gametocytes, in order for man-to-mosquito transmission to occur.

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.

Researchers at the Institut Pasteur in Côte d’Ivoire described the biological mechanisms causing anemia in malaria patients in tropical urban areas. 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.

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.

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

GENETIC AND MOLECULAR STUDIES

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

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. This assay allowed for the first identification of *L. donovani* causing viscerotropic and/or dermatotropic leishmaniasis in Europe.

(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]
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 (18).

The European Commission project [FP-7] Leish-Drug brings together the Institut 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 (19).

**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).

![Detection by immunofluorescence of class II molecules (in green) and H-2M molecules (in red) in murine dendritic cells infected by *L. amazonensis*. The Leishmania parasites are indicated by the white arrows. © Prina, E.; Unité d’Immunophysiologie et parasitisme Intracellulaire / Institut Pasteur](image1)

![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. © Institut Pasteur](image2)

![Cutaneous leishmaniasis on the hand, in Medellin, Colombia. © Rodhain, F. / Institut Pasteur](image3)
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.

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].

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].

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

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 (Triatoma) [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].

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.

**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 neuroschistosomiasis,[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]

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

CLINICAL RESEARCH

The CERMES has been designated to evaluate Niger’s national control program to reduce morbidity due to schistosomiasis 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\(^\text{(8)}\).

A study performed by the Institut Pasteur in Madagascar suggested that \textit{S. haematobium} infection may be linked to decreased sperm quality (sperm apoptosis and a reduced production of seminal fluid)\(^\text{(9)}\).


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.

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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 artemisinin, a treatment whose many years of efficacy may be coming to an end.

At the forefront of such research is a collaborative project linking researchers at the Institut Pasteur in Madagascar and Cambodia and the CERMES in Niger, who use molecular markers (pfmdr1 and pfatp8) 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 arteether-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 pfcr1 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 surprisingly, to dihydroartemisinin (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).

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 chemo prophylaxis 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 RIIN institutes, works to identify and fight the emergence of resistant strains in Africa, Asia, and South America. www.oranet.fr

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抵抗抗生素

细菌可能特别容易发展对设计用来对抗它们的药物的抵抗力，由于水平交换包含遗传物质的质粒。巴斯德研究所研究这些发展，通过其国家抗生素耐药中心，它汇集了“参考菌株”，进行了体外评估新药的有效性，并研究了细菌的耐药机制。在RIIP中，大量研究正在进行，以跟踪这一对公共健康而言是一个显著威胁的方面。

**STUDY FINDINGS**

<table>
<thead>
<tr>
<th>STUDY FINDINGS</th>
<th>INSTITUTE INVOLVED</th>
<th>BIBLIOGRAPHIC REFERENCE</th>
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<tbody>
<tr>
<td><strong>Tuberculosis</strong></td>
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<tr>
<td><strong>Cholera</strong></td>
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<tr>
<td>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.</td>
<td>Pasteur Center in Cameroon</td>
<td>Ngandijo A et al. “Antimicrobial resistance and molecular characterization of <em>Vibrio cholerae</em> O1 during the 2004 and 2005 outbreak of cholera in Cameroon.” <em>Foodborne Pathog Dis.</em> 2008 Nov 9. [Epub ahead of print].</td>
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<td><strong>Plague</strong></td>
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<tr>
<td><strong>Bacterial meningitis</strong></td>
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## Study Findings

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Institute Involved</th>
<th>Bibliographic Reference</th>
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<tbody>
<tr>
<td><strong>Diarrheal diseases</strong></td>
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<tr>
<td>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.</td>
<td>Institut Pasteur in Iran</td>
<td>Aslani MM et al. &quot;Molecular detection and antimicrobial resistance of diarrheagenic Escherichia coli strains isolated from diarrhoeal cases.&quot; <em>Saud Med J.</em> 2008 Mar; 29 (3): 388-92.</td>
</tr>
<tr>
<td>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.</td>
<td>Institut Pasteur in Bangui</td>
<td>Bercion R et al. &quot;Distribution and antibiotic susceptibility of Shigella isolates in Bangui, Central African Republic.&quot; <em>Trop Med Int Health.</em> 2008 Apr; 13 (4): 468-71.</td>
</tr>
<tr>
<td>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 cefotaxime, and high rates for other antibiotics too.</td>
<td>Institut Pasteur in Côte d’Ivoire</td>
<td>Guessennd N et al. &quot;[Qnr-type quinolone resistance in extended-spectrum beta-lactamase producing enterobacteria in Abidjan, Ivory Coast.].&quot; <em>Pathol Biol (Paris).</em> 2008 Nov-Dec; 56 (7-8): 439-46.</td>
</tr>
<tr>
<td><strong>Staphylococci</strong></td>
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<td>Researchers tested naturally occurring antimicrobial peptides derived from amphibian skin against multidrug-resistant strains of common nosocomial infections, including <em>Staphylococcus aureus</em>. All 5 peptides were bactericidal against all bacterial species tested, and 1 peptide was particularly effective in the presence of human serum.</td>
<td>Institut Pasteur – Cenci Bolognetti Foundation</td>
<td>Mangoni ML et al. &quot;Comparative analysis of the bactericidal activities of amphibian peptide analogues against multidrug-resistant nosocomial bacterial strains.&quot; <em>Antimicrob Agents Chemother.</em> 2008 Jan; 52 (1): 85-91.</td>
</tr>
<tr>
<td>A study of 574 clinical isolates of <em>S. aureus</em>, 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.</td>
<td>Institut Pasteur in Madagascar</td>
<td>Randrianirina F et al. &quot;In vitro activities of 18 antimicrobial agents against Staphylococcus aureus strains from Madagascar.&quot; <em>Ann Clin Microbiol Antimicrob Chemother.</em> 2007 May 23rd; 59 (2): 309-12.</td>
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<tr>
<td><strong>Neisseria gonorrhoea</strong></td>
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<td>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.</td>
<td>Institut Pasteur in Ho Chi, Nha Trang, New Caledonia, Bangui, and Madagascar; the Pasteur Center in Cameroon</td>
<td>Cao V et al. &quot;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.&quot; <em>Sex Transm Dis.</em> 2008 Nov; 35 (11): 941-5.</td>
</tr>
<tr>
<td>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 <em>N. gonorrhoeae</em> and <em>N. meningitidis</em> that are associated with reduced susceptibility to penicillin.</td>
<td>Institut Pasteur in New Caledonia</td>
<td>Vernel-Pauillac F et al. &quot;Genotyping as a tool for antibiotic resistance surveillance of Neisseria gonorrhoeae in New Caledonia: evidence of a novel genotype associated with reduced penicillin susceptibility.&quot; <em>Antimicrob Agents Chemother.</em> 2008 Sep; 52 (9): 3293-300.</td>
</tr>
</tbody>
</table>
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, phospholmager)
- BSL-2 + laboratory, including animal facilities
- Recombinant protein production (baculovirus, S. drosophila cells, yeast) and purification (FPLC)

### SCIENTIFIC INSTITUTE OF PUBLIC HEALTH, BELGIUM
- Fungal collection BCCM/IHEM
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 America, and one in the Middle East.

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