

Dengue

Already the world's most prevalent mosquito-borne virus, dengue's increasing incidence and severity qualify it as a worrisome emerging disease.

KEY FACTS

- **2.5 billion** people at risk worldwide
- **50 million** estimated new cases of dengue per year
- **500,000** people require hospitalisation each year, most of whom are children
- Dengue is endemic in more than **100 countries**
Source: WHO

> A disease affecting the world's tropical regions

Transmitted by *Aedes* mosquitoes in tropical and sud-tropical zones of Asia, Africa and the Americas, dengue infects 50 million people every year. Though its classic form causes flu-like symptoms and is not life-threatening, more severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) can be fatal, especially in children and in the absence of medical treatment.

> Environmental changes: an alarming situation

International travel and fast-paced urbanisation in developing countries have contributed to rising incidence and the expansion of affected regions. The United Nations' Intergovernmental Panel on Climate Change has said climatic patterns have exacerbated these trends and will continue to do so in the future.

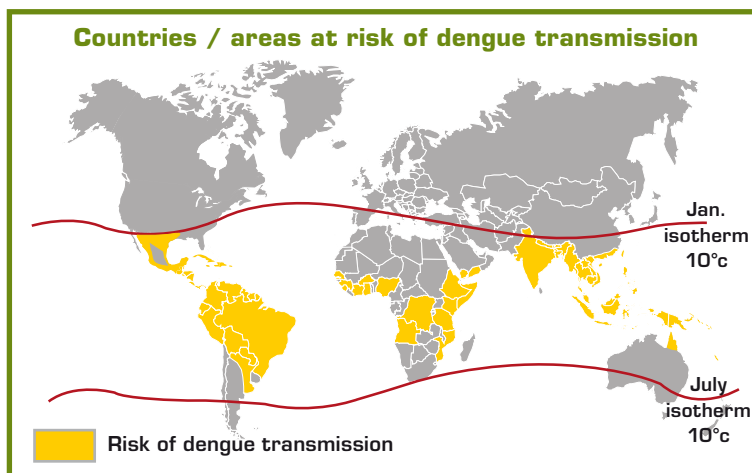
For reasons that are less well understood, the severity of dengue cases seems also to have increased notably in recent years.

> Working toward new preventive strategies

As of the present, there is no specific antiviral medication and no vaccine for dengue, though medical treatment can greatly increase patients' chances of survival, even in the

most severe cases.

Scientists at the Institut Pasteur and in the International Network are working to attack the disease on all fronts by participating in surveillance and diagnosis, proposing a paediatric candidate vaccine, performing basic research on immunological defences and genetic predisposition to severe forms, and working toward a deeper understanding of the mosquito's role in spreading the virus.



Source: WHO, 2007

Institut Pasteur : a worldwide presence



A large portion of the resources of the Institut Pasteur and the International Network is devoted to research and surveillance of infectious pathologies (HIV/AIDS, tuberculosis, malaria) and emerging and re-emerging diseases (SARS, flu, dengue, West Nile fever, rabies, etc.).

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A certified not-for profit private foundation, the Institut Pasteur exercises three missions in the service of the public good since its creation in 1887: research, public health, and training.

At the nexus of several disciplines, including microbiology, immunology and molecular biology, it is one of the foremost centres of biomedical research worldwide. Ten Pasteurian scientists have been named laureates of the Nobel Prize in physiology or medicine.

Open to the world, the Institut Pasteur is at the heart of an International Network of some thirty institutes on every continent, most of which are independent entities governed by their national authorities.

These institutes are associated by partnerships and cooperation agreements covering scientific research, training and public health services, and they share common values and objectives.



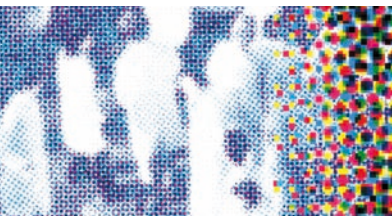
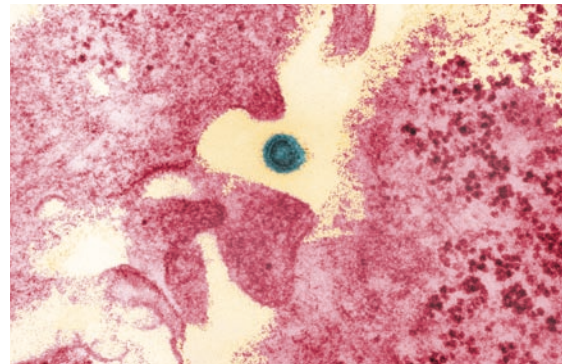


Pathologies

The Institut Pasteur
the Institut Pasteur
International Network
&
Dengue

*"Knowledge belongs
to all mankind"*

Louis Pasteur



Fighting infectious diseases

The Institut Pasteur helps to prevent and treat diseases, especially infectious ones, through research, training and public health activities.



Infectious diseases caused by pathogens (**viruses**, **bacteria**, **parasites** or **fungi**) kill 13 million people worldwide every year.

> Mobilising researchers

The Institut Pasteur and the International Network focus their resources on research into infectious pathologies (HIV/AIDS, tuberculosis, malaria, etc.) and emerging pathologies (SARS, influenza, dengue fever, West Nile fever, etc.).

> Spreading knowledge

To ensure that the results of the research benefit the people concerned, the Institut Pasteur works in close partnership with other research institutions and major public and private institutions at the national and international level. The aim is to contribute to improving human health through basic research, monitoring, and surveillance and by developing new diagnostic tools, medicines and vaccines.

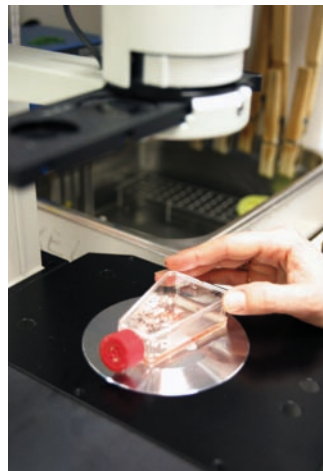
GLOSSARY

Virus : infectious agent, invisible under an optical microscope. Is distinguishable from bacterium because it has only one type of nucleic acid, RNA or DNA.

Bacterium: unicellular micro-organism without nucleus, visible only under a microscope, whose two main shapes are spherical (cocci) or elongated (bacilli).

Parasite : animal or plant organism which lives off its host.

Fungus: filamentous unicellular micro-organism that multiplies in a favourable medium and may cause diseases (aspergillosis, mycoses, etc.).



The disease

USEFUL FACTS

Although the four viral serotypes that cause dengue are closely related, there is no long-term crossed protective immunity and humans can be successively infected by all four.

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated for dengue fever, as they can worsen bleeding.

Climate change and dengue

Climate change is accelerating the spread of dengue fever worldwide. Increased rainfall and warmer temperatures provide ideal conditions for mosquitoes in previously unaffected tropical regions and even in some temperate zones. Droughts associated with climate change can also lead to increased rates of dengue if household water storage techniques provide new breeding sites for mosquitoes.

Mosquito breeding site

Dengue is a mosquito-borne viral disease that most commonly presents as a flu-like illness. However, more severe forms, such as dengue hemorrhagic fever, are on the rise.

> Transmission and epidemiology

Dengue is caused by one of four viral serotypes in the Flavivirus genus (DENV-1, DENV-2, DENV-3, DENV-4). With over 40% of the world's population exposed, it is the most common insect-borne virus, transmitted to humans by the bite of an infectious mosquito in the *Aedes* genus. It is estimated that there are over 50 million new cases of dengue worldwide each year.

In recent years, there has been a sharp increase in cases in Asia, Africa, and especially South America and the Caribbean, where incidence has increased almost tenfold over the past 20 years, according to the Pan American Health Organization. Scientists attribute this resurgence to increased international travel, climate change and unprecedented rates of urbanisation in tropical regions.

> Mild and dangerous forms

The symptoms of dengue are high fever, severe headache, and joint, muscle, and bone pain, sometimes accompanied by nausea, vomiting and rash. The classic form of dengue is serious but rarely life-threatening, lasting 5 to 7 days.

In recent years, severe forms have increased in frequency. Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) can lead to circulatory failure when capillaries become excessively permeable, allowing blood to leak into the abdominal cavity and elsewhere. These forms, which can be fatal in the absence of timely medical intervention, are mostly observed in children.



> Prevention and treatment

There is no vaccine and no specific antiviral treatment for dengue fever. Headaches are treated with painkillers and hydration. Early medical care can greatly increase chances of survival in severe cases by restoring circulatory fluid volume.

At present, control of mosquito populations using environmental management, insecticides, and mosquito larvae predators is the only means currently available for addressing the disease.

Aedes albopictus



Aedes aegypti

USEFUL FACTS

The National Reference Centre for Arboviruses at the Institut Pasteur provides reagents and technology transfers to support teams working on dengue inside and outside the International Network.

GLOSSARY

Plasma extravasation:

seepage of plasma (the liquid component of blood in which blood cells are suspended) from capillaries into surrounding tissue

Serological assays: a set of techniques used to identify the presence of antibodies in blood serum to confirm the presence of an infectious agent

Vector competence:

the ability of arthropods (particularly insects) to acquire, maintain, and transmit microbial agents

Research



Institut Pasteur in Cambodia

Teams at the Institut Pasteur and in the International Network are working on multidisciplinary approaches to dengue, using techniques of basic and applied research in the laboratory and the field.

> Surveillance and epidemiology

Given recent increases in incidence and the spread of dengue to previously unaffected areas, surveillance is essential to understanding and controlling the disease. The International Network participates in surveillance in Asia and the Caribbean region and has investigated or responded to outbreaks in all endemic regions, including French Guiana, Côte d'Ivoire, Paraguay, New Caledonia, Madagascar and Cape Verde.

Scientists have also studied virus circulation using molecular epidemiology at the Institut Pasteur in Cambodia and genetic analyses of viral isolates obtained in the Network and metropolitan France, shedding light on the potential for future outbreaks.

> Understanding transmission cycles

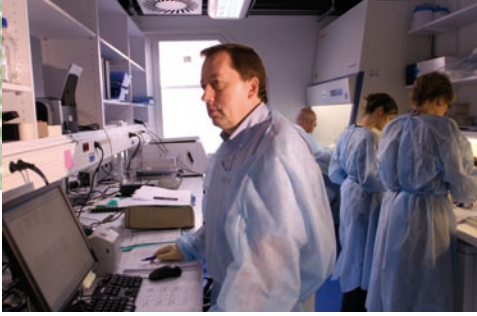
Scientists at the Instituts Pasteur in French Guiana and Dakar collaborated in the study of possible animal reservoirs for the virus in West Africa and South America, demonstrating for the first time that neotropical wild mammals can be infected with dengue.

At the Institut Pasteur in Guadeloupe, epidemiologists studied the role of the environment, urbanisation, and climate in dengue risk in a multi-disciplinary collaboration with local and international partners.

> Improving diagnostic techniques

The Instituts Pasteur in French Guiana and Dakar with the Institut Pasteur evaluated diagnostic tools based on the detection of the NS1 antigen in patients in the early stages of the disease, finding them suitable for first-line use in the field.

The Institut Pasteur in Cambodia collaborated with the WHO/TDR program to evaluate IgM tests and is now assessing NS1 diagnostic tests.



The National Reference Centre for Arboviruses at the Institut Pasteur is charged with surveillance of imported cases of dengue.

> Entomology

A collaborative project involving the Institut Pasteur and the Instituts Pasteur in French Guiana and Guadeloupe is studying the role of *Aedes aegypti* in spreading the virus and risk factors of transmission in the Caribbean region. Scientists at the Institut Pasteur in Dakar studied changes in the viral genome caused by passage through the *Aedes aegypti* mosquito, as well as the genetic diversity of the species and the vector competence of local mosquito populations.

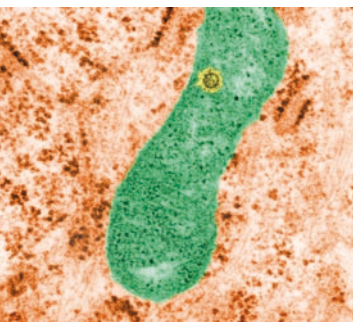
> Genetic susceptibility to severe dengue disease

Scientists at the Institut Pasteur discovered a gene variant found in 10% of Asians, 20% of Caucasians and 40% of Africans that can protect against the development of severe dengue disease. Further studies are underway with the International Network and outside partners to understand genetic susceptibility to dengue and regional variance in disease severity.

> The search for new resistance mechanisms

At the Pasteur – Hong Kong University Research Centre, researchers used a screening platform to identify some twenty potential inhibitors of viral replication in partnership with the University College of London and the Shanghai Institute for Materia Medica.

The Institut Pasteur in Cambodia is studying symptomatic and asymptomatic cohorts to shed light on the early stages of anti-dengue immunity.



Murine neural cells infected by the dengue-1 virus.

Severe forms of the disease

The Institut Pasteur in Cambodia is collaborating with the health service of the French army to study mechanisms of plasma extravasation, a dangerous symptom of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). This work may lead to the development of new treatment targets.

Economic impact of dengue

In another project financed by the Paediatric Dengue Vaccine Initiative (PVDI), scientists studied the incidence and economic impact of dengue in Cambodia, demonstrating that dengue and other febrile illnesses pose a significant financial burden to households.

DENFRAME: A comprehensive approach to dengue

The **DENFRAME** project (2005-2009), financed by the European Union, brought together 13 laboratories, including five institutes in the Institut Pasteur International Network: the Instituts Pasteur in Cambodia, Ho Chi Minh City, and French Guiana, the University of Hong Kong-Pasteur Research Centre, and the Institut Pasteur. Its main achievements were:

- Creation of an extensive electronic database of clinical and biological data
- Implementation of reference techniques for virological and immunological diagnosis
- Production of a recombinant dengue virus envelope protein for serological assays
- Identification of several compounds, including an antibiotic derivative, which selectively inhibit viral replication

The success of this project has led its members to pursue their work, which is set to continue with new partners around the world.

Perspectives

Pasteur scientists are working to provide new answers to the large – and growing – problem of dengue.

> Improving diagnostic techniques

Given dengue's non-specific symptoms and the risk of serious health consequences, early and accurate diagnosis is essential. Among the problems to be solved are “false positives,” the optimisation of existing tests for use in the field, and the development of more sensitive and specific serological assays.

The Institut Pasteur, working with the Institut Pasteur in French Guiana, has developed new serological tests specific to each dengue serotype capable of early detection of immunoglobulin molecules.

> The search for a paediatric vaccine

Vaccine research for dengue is particularly challenging due to the lack of an animal model and the fact that the disease is caused by four different viruses. Many candidate vaccines have been proposed but none has yet been approved.

Researchers at the Institut Pasteur, in collaboration with CNRS (the French agency for scientific research), have developed a new paediatric candidate vaccine based upon the measles vaccine. It has been shown to stimulate the production of specific antibodies, which may be expanded so as to act upon all four viruses. This vaccine is currently undergoing preliminary testing.

> Resistance mechanisms and immunological defences

Researchers at the Institut Pasteur and in the International Network are working to better understand the interaction between dengue and the body's defences, including genetic mutations affecting innate immunity to viral infection and the 3D structure of proteins on the virus' surface that interact with human antibodies.

> The role of the mosquito

As no specific treatment exists for dengue, prevention of the disease is especially important. Research teams at the Institut Pasteur are studying interactions between mosquitoes and viral genomes, as well as other aspects of vector control, including potential mechanisms for using the insects to control – instead of spread – the dengue viruses.



In 2011, the Institut Pasteur will inaugurate a new €60 million building dedicated to the study of emerging infectious diseases. The facilities will allow for multidisciplinary research including cellular and molecular imaging, structural biology, and genomics.

Institut Pasteur units working on dengue

- Unit on Flavivirus-Host Molecular Interactions
- Laboratory on Viral Genomics and Vaccination
- Unit on the Molecular Genetics of Bunyaviruses
- Unit on Molecular Prevention and Therapy of Human Diseases
- Unit on Viral Pathogenesis
- Unit on Structural Virology
- Unit on the Epidemiology of Emerging Diseases
- National Reference Centre on Arboviruses

Members of the International Network working on dengue

- Institut Pasteur in Côte d'Ivoire
- Institut Pasteur in Dakar, Sénégal
- Institut Pasteur in New Caledonia
- Institut Pasteur in French Guiana
- Institut Pasteur in Cambodia
- Institut Pasteur in Guadeloupe
- Institut Pasteur in Ho Chi Minh City, Vietnam
- Institut Pasteur – Hong Kong University Research Centre