

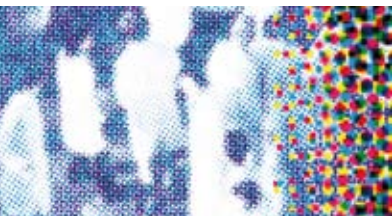
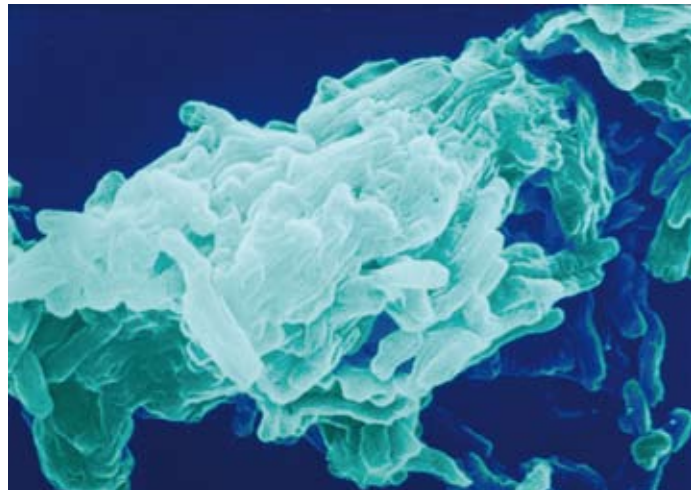


Pathologies

The Institut Pasteur
the Institut Pasteur
International Network
&
Tuberculosis

*"Knowledge belongs
to all mankind"*

Louis Pasteur



Fighting infectious disease



The Institut Pasteur works 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.

> Mobilizing researchers

The Institut Pasteur and the International Network focus their resources on research into infectious pathologies (HIV/AIDS, tuberculosis, malaria, etc.) and emerging diseases (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 ordinary optical microscope. Viruses are distinguishable from bacteria because they have only one type of nucleic acid, RNA or DNA.

Bacterium: unicellular micro-organism without a nucleus, visible 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 environment and may cause disease (aspergillosis, mycoses, etc.).





Tuberculosis

KEY FACTS

Nearly 2 million deaths and over **9 million new cases** each year.

The most affected regions are sub-Saharan Africa and the highly populated zones of Asia (India, Bangladesh, China, Indonesia, etc.).

One person in the world becomes infected with TB **every second**.

Tuberculosis is the **leading cause of death** among AIDS patients in Africa.

GLOSSARY

Genetic susceptibility: predisposition of an individual to be affected by certain diseases on the basis of their genetic inheritance.

"W-Beijing" strains: a family of particularly contagious *M. tuberculosis* strains associated with high virulence and multiple antibiotic resistance.

Tuberculosis is an infectious disease that occurs most commonly in the pulmonary form. It causes fever, weight loss and coughing, sometimes accompanied by blood-tinged sputum. If left untreated, death occurs within a few months.

At the end of the 20th century, it was thought that tuberculosis was under control in the developed world, but the AIDS epidemic and an upsurge in antibiotic-resistant bacilli have contributed to the current worsening of the global epidemiological situation.

> A global scourge

Currently, two billion people are carriers of the tuberculosis bacillus (Koch's bacillus), but only 5 to 10% of them will develop the disease over the course of their lifetime. Tuberculosis mainly affects people living in developing countries, where 98% of deaths from the disease occur.

New treatment-resistant forms of the disease, which are responsible for 500,000 new cases each year, are causing concern in the medical community and leading to fears of an epidemic that would be unresponsive to the medicines currently available.

> State-of-the-art research and international collaboration

Scientists working at the Institut Pasteur and in the International Network are conducting research to improve diagnosis, discover more effective antibiotics and develop stronger vaccines.

A dozen institutes from the International Network are participating in national programmes for the control of the disease. A number of them are involved in the WHO's "Global Laboratory Initiative" (GLI), which aims to build capacities at national laboratories, particularly with respect to tuberculosis.

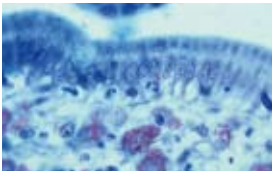
> Significant progress

The latest anti-TB drug was developed in the 1970s but recent discoveries in genetics and genomics have opened up new prospects for treatment. These medicines will need to be active against antibiotic-resistant strains and come in the form of combinations that reduce the length of treatment. Health authorities, for their part, will need to improve monitoring and prevention activities at the population level.

Every year, 500,000 cases of "multi drug-resistant" tuberculosis occur (5% of the total number of new infections).

While the pulmonary form remains the most common, tuberculosis can also affect the bones, kidneys, intestines, genitals, meninges and skin.

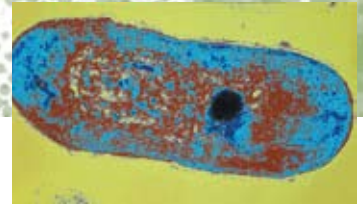
Tuberculosis & HIV/AIDS: a highly dangerous co-infection



Concomitant intestinal tuberculosis and microsporidiosis in an HIV-positive individual.

HIV and TB are extremely virulent when present together.

Tuberculosis is responsible for the deaths of one-third of AIDS patients worldwide. In countries where the epidemic is widespread, HIV-positive people have a 20-fold greater risk of developing tuberculosis than their HIV negative peers. It is estimated that between 1993 and 2003, this co-infection caused the deaths of 230,000 people in over 100 countries where there is epidemiological surveillance, particularly in sub-Saharan Africa.



The disease

Tuberculosis is a contagious disease caused by a bacterium, *Mycobacterium tuberculosis*, also called Koch's bacillus, which is spread by airborne transmission.

Once greatly feared under the name "consumption," tuberculosis may again become a disease impervious to existing medicines if newly-appeared resistant forms continue to spread. The emergence of HIV/AIDS and international migration have worsened the global epidemic.

> Transmission and spread

The TB bacillus is present in the fine droplets projected by sneezing, coughing or spitting. A person with an "infectious and active" form of the disease can therefore infect several dozen people over the course of a year.

> A common disease in disadvantaged populations

Tuberculosis is sometimes said to be a "social" disease because it spreads among underprivileged communities (those with precarious living conditions, poor hygiene, and an absence of health facilities for prevention and health education). Developing countries and underprivileged populations in developed countries are most affected by this epidemic.

> Mutant strains

Health authorities are particularly concerned about two current trends.

First, "multi drug-resistant" tuberculosis, which is refractory to standard antibiotics, has been reported on every continent. Half of the 500,000 cases worldwide are concentrated in the former Soviet bloc, China, India and Africa. These mutant strains are extremely difficult to control, with a 100-fold greater cost in antibiotics compared to tuberculosis caused by treatment-sensitive bacilli.

Second, "extensively drug-resistant" tuberculosis is also resistant to the second-line antibiotics known as fluoroquinolones and injectable anti-tuberculosis agents. This form of tuberculosis was responsible for some 50 deaths in South Africa in 2006; other cases have been reported in all regions of the world. The WHO, in response to this "major public health threat," created a working group on extensively drug-resistant tuberculosis in 2006.



HKU-Pasteur Research Centre

In 2009, with more than **11,000 article citations** on tuberculosis, the Institut Pasteur was ranked first among the top 20 scientific research institutes working on this disease.
www.sciencewatch.com

Research

Units working on tuberculosis at the Institut Pasteur

- Mycobacterial Genetics
- Integrated Mycobacterial Pathogenomics (candidate unit)
- Immune Regulation and Vaccinology
- Structural Biochemistry

Basic research: interaction of the bacillus with human cells

A team of researchers from the Institut Pasteur is studying the genetic diversity of the different strains of tuberculosis and its impact on the progression of the disease. Studies on response to infection have shown that the bacillus and its human host have a considerable faculty for reciprocal adaptation. Studies have also been conducted on the bacterium's capacity for genome rearrangement and DNA recombination, repair and renewal, revealing the many "faces" of the bacillus.

Sequencing the genome of *Mycobacterium tuberculosis* and identifying the functions of its genes have opened new avenues for tuberculosis control.

> Further work on the genome

In 1998, the Institut Pasteur and the Sanger Centre in the United Kingdom completed the sequencing of the tuberculosis bacillus genome. The "decoding" of its 4,000 genes opened the way for exploratory studies that are currently underway in many countries around the world. The Institut Pasteur is continuing to develop genetic tools to identify the functions of the bacillus' genes, including those responsible for its virulence.

In addition, the Institut Pasteur's research teams have recently begun new research into genetic predisposition (susceptibility).

> Detection of the "dormant" bacillus

A research team from the Institut Pasteur has recently shown that the tuberculosis bacillus is able to lie dormant in the host's fat cells. This allows it to shelter from attack by the immune system or powerful antibiotics before reactivating itself several years after the initial contamination.

This discovery has opened the way for new targeted therapeutic research.

A powerful tool in Guadeloupe

The researchers at the Institut Pasteur in Guadeloupe have created a database of over 71,000 strains originating from 160 countries. They are analysing the genetic variations of the tuberculosis bacterium with a view to establishing its relationship to population movements. The tuberculosis laboratory at the Institut Pasteur in Guadeloupe recently joined WHO's network of supra-national laboratories.

> New diagnostic tools

The examination of sputum under the microscope remains the standard method for detecting tuberculosis. Although it is quick to perform, this method is not very sensitive.

Scientists at the Institut Pasteur are developing tests designed to detect substances secreted by the bacillus very early on after infection or produced as a result of the patient's immune response. In addition, amplification methods have made it possible to detect the presence of the bacterium's genes and to identify resistance to antibiotics.

> Surveillance and research

The Institut Pasteur International Network has set up tools for epidemiological and microbiological surveillance of tuberculosis.

In Cameroon, Algeria, Madagascar and the Central African Republic, the Network is in charge of investigations into resistance to anti-tuberculosis drugs. In collaboration with the Institut Pasteur, it is conducting research on the mechanisms of acquiring resistance acquisition in terms of genetic susceptibility. The Institut Pasteur and the Institut Pasteur Korea are jointly studying the immune responses of infected cells and the impact of the genetic diversity of the bacillus on these mechanisms.



Students attending a course on tuberculosis organised by the Institut Pasteur International Network in Shanghai.

> Knowledge transfer

In Paris and Shanghai, the International Network offers courses on new molecular technologies for diagnosis, detection of antibiotic resistance and the study of human-to-human transmission. These training courses are open to researchers from all over the world and are organised together with the CDC and Fudan University in Shanghai.

Furthermore, the Institut Pasteur in Algeria provides medical mycobacteriology training for laboratory technicians and managers in French-speaking African countries.

Finally, the Institut Pasteur has set up a group of experts in the diagnosis of tuberculosis, which hosts and trains students interested in the subject.

Genetic diversity of tuberculosis

A team from the Institut Pasteur is using a functional genomics approach to understand the genetic diversity of *Mycobacterium tuberculosis* and its relationship with the host's immune response, in partnership with the CNRS, the CDC in China and Fudan University, Shanghai.

International cooperation

Many institutes belonging to the Institut Pasteur International Network are involved in research into tuberculosis:

- Pasteur Centre in Cameroon
- Institut Pasteur in Algeria
- Institut Pasteur in Bangui, Central African Republic
- Institut Pasteur in Cambodia
- Institut Pasteur in Côte d'Ivoire
- Institut Pasteur in Dakar, Senegal
- Institut Pasteur in Guadeloupe
- Institut Pasteur in Ho Chi Minh City, Vietnam
- Institut Pasteur Korea
- Institut Pasteur in Lille, France
- Institut Pasteur in Madagascar
- Institut Pasteur in Morocco
- Institut Pasteur in Saint Petersburg, Russia
- Institut Pasteur in Tunis, Tunisia

Future prospects: a more effective vaccine, a greater variety of antibiotics

Control methods

The "BCG" (bacillus Calmette Guérin) vaccine was used for the first time in 1921 by Pasteurian physicians Albert Calmette and Camille Guérin. Though it is vital in preventing serious forms of the disease in young children, it only protects one in two adults from pulmonary tuberculosis. Its current form is no longer sufficient to prevent transmission of the disease and stamp out the global epidemic.

Drug treatments

In order to be effective, current antibiotic treatments must be pursued for 6 to 24 months, depending on the sensitivity of the strain to anti-tuberculosis drugs. The length of the treatment is a common obstacle to good patient compliance; it is therefore imperative to find shorter treatments.

Promising avenues

Following in vitro testing, researchers are now carrying out toxicity tests on new TB-inhibiting products to ensure that they can be combined with the usual antibiotics. The initial data collected appears to confirm hopes for a new compound that could be used to develop anti-tuberculosis drugs 100 times more potent than those currently available.

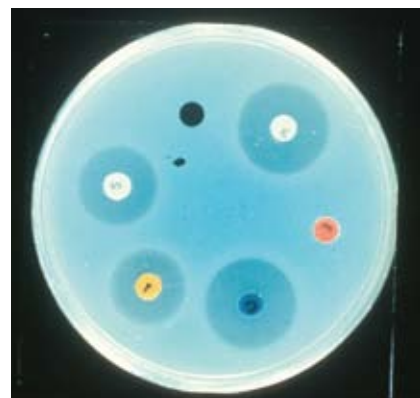
Collaborative efforts bear fruit

As part of the European "TB-VIR" project, the Institut Pasteur Korea and the Pasteur Institute are working in partnership with a number of research institutes (CNRS, Institut Pasteur, GATC, Max Planck Institute, the University of Zaragoza) on tuberculosis caused by bacilli from the "W-Beijing" family, which are responsible for several epidemics of multi drug-resistant tuberculosis. This research should facilitate modelling of potential epidemics and planning of appropriate responses.

A previous European project, TB Vaccine Cluster, brought together 36 European laboratories under the coordination of the Institut Pasteur. During this project, scientists from the Institut Pasteur and the University of Zaragoza discovered that the inactivation of a single gene produces a bacillus that is more attenuated than the BCG strain. This work has led to the development of a new vaccine candidate, a project that is being pursued as part of the "TB - VAC" and "NEW TB - VAC" projects.



The Institut Pasteur in Dakar (Senegal)



Antibiograms test the sensitivity of bacilli to different antibiotics.

Institut Pasteur: a worldwide presence



A researcher from the Institut Pasteur is on loan to WHO as part of a programme to build laboratory capacity with respect to tuberculosis.

A not-for-profit private foundation, the Institut Pasteur performs research, education and public health activities in the public interest since its creation in 1887.

At the nexus of several disciplines, including microbiology, immunology, and molecular biology, it is recognized worldwide for its contributions to biomedical science.

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The Institut Pasteur is at the core of an International Network of some thirty institutes on all five continents, most of which are independent entities governed by their national authorities.

The institutes of the International Network are associated in partnerships and cooperation agreements covering scientific research, training and public health services, and they share common values and objectives.

