



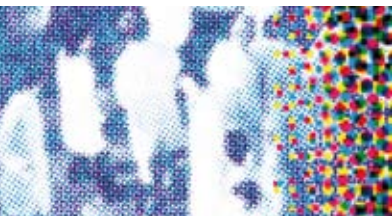
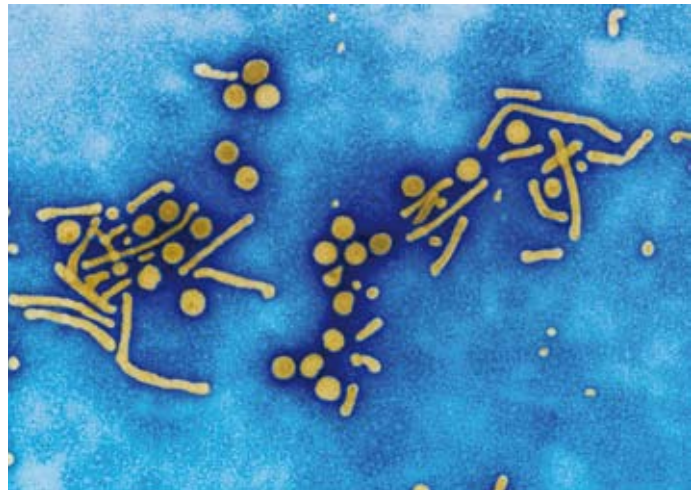
Pathologies

The Institut Pasteur  
the Institut Pasteur  
International Network

**Viral Hepatitis**

*"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, hepatitis, 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.).



# Viral hepatitis

Viral hepatitis is an infectious disease of the liver that can evolve towards cirrhosis or liver cancer.

## FOR INFORMATION

Worldwide, chronic hepatitis affects:

- **370 million people** infected with HBV
- **170 million people** infected with HCV

These people have a heightened risk of dying of cirrhosis or liver cancer, diseases which are responsible for **a million deaths worldwide each year.**

## Hepatitis and HIV coinfection

Many HIV-positive individuals also carry hepatitis viruses B, D (delta) and/or C. Because their immune system is weakened, they run a greater risk of developing lesions on the liver or liver cancer. Such co-infections are also a source of problems because of interactions between treatments.

## > Viruses that are widespread

To date, five viruses are known to cause hepatitis: A, B, C, D (or delta), and E. Over 1 million cases of hepatitis A are recorded in the world each year and it is one of the primary causes of acute hepatitis in industrialised countries. Hepatitis E, which causes similar symptoms, is less common in these countries than in the developing world.

The hepatitis B virus is estimated to have already infected one third of the global population. In developing countries, it is estimated that 5 to 15% of persons are chronic carriers, whereas only about 1% of the population is chronically infected in North America and Western Europe. People infected with this virus may also become infected with hepatitis D.

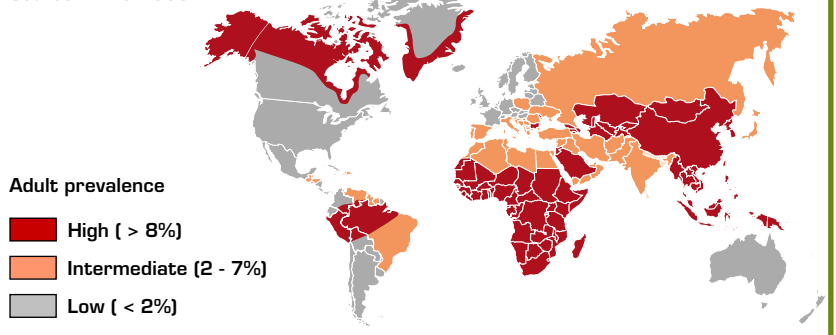
Hepatitis C, which is less common but sometimes more severe, appears to affect 3% of the global population.

## > Research challenges

Currently, there is no treatment for acute hepatitis. The efficacy of antiviral agents used for chronic cases has sometimes been questioned, and only hepatitis A, B and D (delta) can be prevented by vaccination. Research conducted at the Institut Pasteur and in the International Network aims to improve tools for early diagnosis and develop new treatments or vaccines.

## Hepatitis B prevalence, 2005

Source: WHO 2005



**HCV was identified in 1989.** Previously, it was designated “non A non B hepatitis.”

In France, **it is mandatory to report the diagnosis of hepatitis A and acute (symptomatic) hepatitis B** to health authorities.

## Multiple pathologies

Beginning in the second half of the 20th century, scientists identified five different viruses that cause hepatitis. Designated by the letters A, B, C, D (or delta), and E, they differ in their mode of transmission and potential pathogenicity.

### > Common features...

All hepatic viruses penetrate liver cells, known as hepatocytes, where they go on to multiply. The immune system then destroys the infected cells, thus causing liver inflammation. Symptoms last for several weeks but do not appear in all cases. They may be confused with flu symptoms (fever, joint and muscle pain, fatigue, loss of appetite), and are sometimes accompanied by abdominal pain, nausea, and vomiting. Clinical signs induced by liver inflammation may also include jaundice (yellow discolouration) in the skin and/or eyes, dark urine and pale faeces.

### > ... and specific characteristics

These viruses can be differentiated by a number of criteria, including mode of transmission, incubation period, and potential for becoming chronic infections.

Virus	Transmission routes	Vaccine	Incubation	Evolution towards chronicity	Co-infection
Hepatitis A, HAV	Faecal-oral route	Yes	30 - 40 days	No	-
Hepatitis B, HBV	Via blood, sexual transmission, mother to child	Yes	40 - 180 days	Adults : 5%, newborns : 90%	Worsened by hepatitis D
Hepatitis C, HCV	Via blood	No	30 - 180 days	50 - 85%	Common with HIV
Hepatitis D or delta	Via blood, sexual transmission	Hepatitis B vaccine	30 - 90 days	Yes	Only appears with hepatitis B
Hepatitis E, HEV	Faecal-oral route	No	20 - 60 days	No	-

### > Chronic forms and complications

Most types of hepatitis present as benign forms that spontaneously resolve themselves in the body. However, some viruses (hepatitis B, C) can lead to the development of chronic liver disease. Years later, patients may suffer from hepatic fibrosis, cirrhosis or even liver cancer. When accompanied with other pathologies affecting the liver (other viruses with liver tropism or HIV), the risk of an unfavourable outcome is greatly increased. Finally, some viruses can cause acute liver failure, a condition that is rare but almost always fatal (hepatitis A, B, E).

### > Vaccines and treatments

A vaccine against hepatitis A has been available since 1992 and is recommended for non-immunised adults and children one year or older travelling to endemic areas. Since 1981, highly effective vaccines have been available against hepatitis B (and D), including the GenHevac B vaccine developed by the Institut Pasteur. The chronic forms of hepatitis B and C, responsible for liver fibrosis, can be treated by specific antivirals (tenofovir) for HBV and by a combination of interferon and ribavirin for HCV, with recovery rates of 40-80%. There is no vaccine against HCV and no specific drug for the treatment of acute hepatitis (early antiviral treatment is recommended).

## FOR INFORMATION

**The French National Agency for Research on AIDS and Viral Hepatitis (ANRS)** is the main agency in charge of the coordination and funding of research on HIV/AIDS and hepatitis B and C in France. It is also involved in research programmes in developing countries.



*Researchers developed a vaccine against hepatitis B at the Institut Pasteur.*

## GLOSSARY

### **Carcinogenesis:**

conversion of a normal cell into a cancer cell.

**Cytoskeleton:** dynamic structure in the cell that serves to maintain its form and that confers most mechanical properties (intracellular transport, mitosis or cell division, cellular motion, etc.)

## Research

The Institut Pasteur and the International Network are contributing to the fight against viral hepatitis and its complications via numerous research projects.

### > Basic research

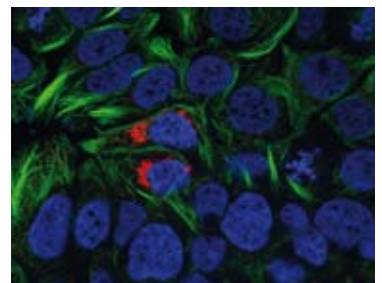
At the Institut Pasteur in Lille, research teams are seeking to understand the molecular mechanisms of HCV's entry, replication and assembly in host cells, as well identify the cell receptors involved. In Athens, the Institut Pasteur in Greece has identified a new viral protein which appears to be involved in HCV's interaction with the host cell.

### > Diagnosis and diagnostic tools

Since viral hepatitis is often asymptomatic, diagnosis can pose a particular challenge to clinicians. Research groups in Paris, Dakar, Bangui and Cameroon are therefore collaborating to identify markers of HBV infection in early childhood. In Romania, the Cantacuzino Institute, which houses a national reference laboratory for viral hepatitis, is working to standardise diagnostic procedures in order to rationalise the sometimes contradictory results of current tests.

### > The entry of HCV in host cells

Researchers in the Unit on Hepacivirus and Innate Immunity at the Institut Pasteur have demonstrated the role of microtubules, key components of the "cytoskeleton," in the entry of the hepatitis C virus into cells and the infection that follows. Other studies on the entry of HCV into hepatic cells have led Pasteur scientists to identify a natural inhibitor of infection that acts upon the lipoproteins associated with viral particles.



*Human liver cells infected with the hepatitis C virus. Microtubules appear in green, nuclei in blue and viral particles in red.*

## Pasteurian collaboration on HCV

An international HCV research programme conducted by the Institut Pasteur International Network is currently under way on several continents. Coordinated by the Institut Pasteur in Greece, it mobilises research teams in Ho Chi Minh City (Vietnam), Cambodia, Saint Petersburg (Russia), and Cameroon.

## A new research site in Egypt

Egypt has one of the world's highest prevalence rates for hepatitis C. Since 2001, a Franco-Egyptian collaboration network on hepatitis has been supported in Egypt by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS). With the involvement of several research groups from the Institut Pasteur, including the Unit on the Epidemiology of Emerging Diseases, the project has led to the creation of a dedicated research site in Cairo in 2007. Researchers focus on viral transmission, the evaluation of treatments, and acute infection (diagnosis, spontaneous elimination of the virus and risk factors). [www.hepegypt.org](http://www.hepegypt.org)



Researchers from Ain Shams University in Cairo collaborate with the Institut Pasteur on viral hepatitis.

## > Mechanisms of immunity

Researchers from the Institut Pasteur in Morocco are studying genetic predisposition to HBV and HCV infection. Other teams are studying the immune response to various viral proteins in infected subjects and the continued presence of the virus in chronic infections. Researchers are also measuring the impact of genetic recombination in hepatitis B and C viruses on the evolution and therapeutic management of chronic forms of the disease.

Finally, scientists are working to identify immunological determinants of spontaneous recovery, as well as the role of certain immune cells in individuals exposed to HCV who do not become infected.

## > Research on epidemiology

In Morocco and Tunisia, researchers are currently assessing the impact of vaccination on the epidemiology of hepatitis B, ten years after the start of a major vaccination campaign in both countries.

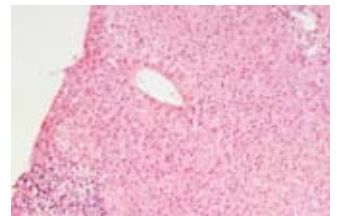
In partnership with research groups in Algeria and Iran, they are also studying the epidemiology of hepatitis E in the region, of which little is known, to evaluate the risk for epidemic flare-ups.

In pregnant women, this infection can be responsible for acute liver failure, particularly during the third trimester.

## Mechanisms of carcinogenesis

In Paris, researchers are studying the molecular mechanisms leading to liver cancer both in humans and in animal models. In particular, members of the laboratory associated with the National Reference Centre for viral hepatitis B, C and Delta are looking for proteins specifically expressed in subjects with liver carcinoma.

In North Africa, several institutes are jointly conducting clinical research on the causes and factors of hepatocellular carcinoma and the genetic mechanisms involved in carcinogenesis.



Histological section of a liver infected by hepatitis C.

## HAV in Madagascar

The Institut Pasteur in Madagascar has demonstrated virtually universal exposure to HAV among subjects above the age of 10 in Antananarivo, despite recent improvements in sanitation.

## The search for a vaccine against HCV

Researchers at the Institut Pasteur and at the Institut Pasteur in Iran are exploring new leads in fundamental biology that could lead to the discovery of a vaccine against hepatitis C.



The vaccination centre at the Institut Pasteur in Bangui, where vaccines for hepatitis A and B are available.

## Perspectives

Ongoing research is opening new avenues to improve both prevention and treatment of viral hepatitis.

### > Finding a vaccine for hepatitis C

The genetic diversity of HCV has for many years constituted an obstacle to the development of an effective vaccine. However, several groups have been able to identify constant factors within this diversity, thanks to the development of bioinformatic tools applied to the structure of HCV proteins and variability analyses of the viral genome. This work - conducted in Paris, Ho Chi Minh City, Saint Petersburg, Greece, Iran and Romania - offers promising prospects for the development of a vaccine.

### > Improving the treatment of chronic forms

A new therapeutic vaccine candidate developed by the Laboratory on Hepatitis Virus B Pathogenesis at the Institut Pasteur is currently the subject of a clinical trial (phase II) under the aegis of the ANRS. It is a combination of a DNA vaccine and antiviral agents. In addition, the Unit on the Epidemiology of Emerging Diseases is coordinating a randomised controlled trial to test the effectiveness of a similar therapeutic strategy in Senegal.

Finally, a research group in Paris is studying the various stages of the hepatitis C virus' life cycle. The scientists' aim is to obtain chimeric viruses from HCV and another virus responsible for hepatitis in small primates, in order to better evaluate antiviral agents using animal models.

### The hypothetical hepatitis F virus:

it is thought that an as yet unidentified virus may be responsible for certain cases of acute liver failure in patients who are negative for all other hepatitis viruses. Without a liver transplant, most of these cases are fatal. The list of hepatitis viruses may still grow in the future.

### Institutes in the International Network conducting research on hepatitis

- Pasteur Centre in Cameroon
- Institut Pasteur in Algeria
- Institut Pasteur in Bangui, CAR
- Cantacuzino Institute, Romania
- Institut Pasteur in Dakar, Senegal
- Institut Pasteur – Cenci Bolognetti Foundation, Italy
- Institut Pasteur in Greece
- Institut Pasteur in Ho Chi Minh City, Vietnam
- Institut Pasteur in Iran
- Institut Pasteur in Lille, France
- Institut Pasteur in Madagascar
- Institut Pasteur in Morocco
- Institut Pasteur in Saint Petersburg, Russia
- Institut Pasteur in Tunis, Tunisia

### Units working on hepatitis at the Institut Pasteur

- Unit on the Epidemiology of Emerging Diseases
- Unit on Hepacivirus and Innate Immunity
- Unit on Viral Immunopathology
- Laboratory on Hepatitis Virus B Pathogenesis
- Laboratory associated with the National Reference Centre (CNR) for Hepatitis B, C and Delta - INSERM U785

# Institut Pasteur: a worldwide presence

The Institut Pasteur and the International Network work in close collaboration with the WHO.



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.

