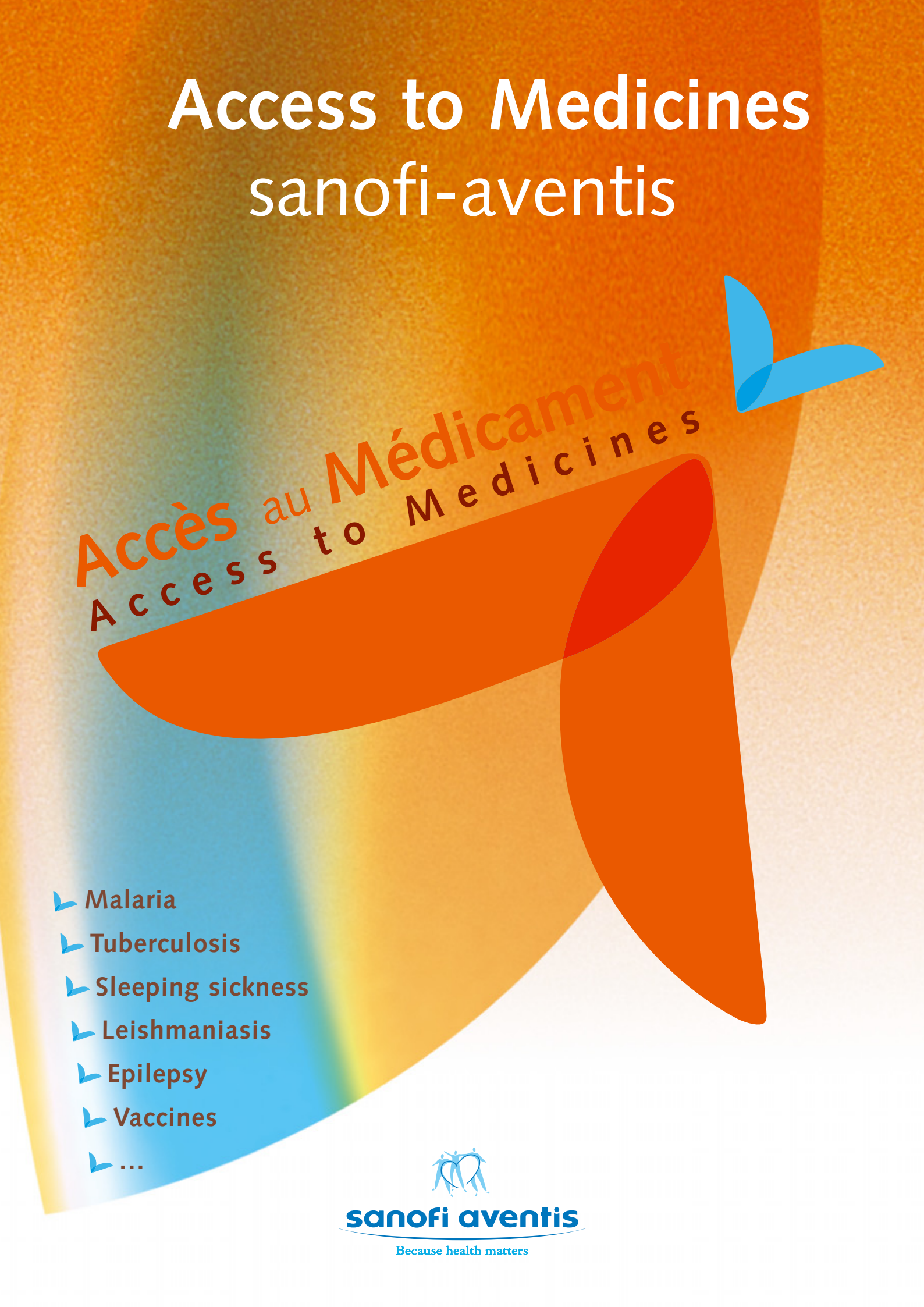
Access to Medicines
sanofi-aventis



- Malaria
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- Sleeping sickness
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- ...

sanofi aventis

Because health matters

Contents

Jean-François Dehecq
Chairman

"80% of the world's population has little or no *access to medicines.*
The pharmaceutical industry must rise to this challenge.

At sanofi-aventis, we take action through practical initiatives. Therefore, we have identified six areas that constitute serious public healthcare concerns in the Southern hemisphere and in which the group has a history of pharmaceutical expertise:

- Malaria
- Tuberculosis
- Sleeping sickness
- Leishmaniasis
- Epilepsy
- Vaccines.

However, as an industrial company, we also aim to further local economic development in countries of the Southern hemisphere, and we are committed to maximizing our presence there.

The future of the pharmaceutical industry is at stake; if these challenges are not met, it will no longer exist. At sanofi-aventis, we are committed to playing an active role in access to medicines."

sanofi aventis
Because health matters

Accès au Médicament
Access to Medicines

Dr. Robert Sebbag

Vice President Access to Medicines

Why has Europe's top-ranking pharmaceutical company, one of the world leaders, launched an « Access to Medicines » program?

Sanofi-aventis is committed to protecting health and to serving the needs of patients.

Eighty per cent of the world's population has no access to healthcare and medicines, and this situation is unacceptable. There are of course many reasons for this state of affairs, but a major healthcare player such as sanofi-aventis must take action. Medicines alone do not define healthcare policies, but public healthcare policies cannot be implemented without quality medicines.

Sanofi-aventis has nearly 100,000 employees in 80 countries worldwide; access to medicines is limited in many of these countries. Reports from our people in those countries have prompted our response to their most urgent healthcare needs. The group has thus made sustained development and access to medicines key components of its strategy.
Sanofi-aventis has manufacturing facilities in many countries in the Southern hemisphere. These plants must continue their operations, while increasing and improving production, thereby promoting development and maintaining employment in these countries.

To take action in these fields, the Group decided to establish an Access to Medicines Division, which draws upon our know-how in the following areas:

- Research and Development.
- Implementing new treatment strategies and improving treatments which are currently available.
- Information, Education and Communication at all stages of the healthcare process; as we say, « right down the chain to the very last link ».
- Implementing pricing and distribution policies which help facilitate access to medicines.

This brochure presents our proposals and initiatives in combating five diseases where our experience can provide legitimate and effective help: malaria, tuberculosis, sleeping sickness, leishmaniasis and epilepsy. Other initiatives, programs and large-scale prevention projects involve the Group's vaccines division, world leader in the field. In this way, we combine treatment and prevention.

This ambitious program could not - and will not - move forward without a strong **partnership** policy. By partners we mean all public or private national, international and multilateral organizations that play a role in ensuring better access to healthcare in countries of the Southern hemisphere.

OUR MISSION

The Access to Medicines department coordinates and implements sanofi-aventis' initiatives in the fight against certain diseases that represent real public health issues and about which we have some expertise.

Our mission is an integral part of the Group's strategy and covers 3 main areas:

- **Preferential pricing policy (no profit-no loss)**
- **Improvement of existing drugs**
- **Information, Education and Communication**

We work closely with operational teams. Our activities are in line with the Group's sustainable development policy and help ensure continuous employment in our industrial plants in developing countries.

The entire team in the « Access to Medicines » Division is deeply committed to the Group's continued efforts in promoting better health for patients worldwide and to satisfy unmet healthcare needs. At sanofi-aventis, this Access to Medicines policy is part of our overall Group strategy; it is not a mere device to enhance our corporate image, but exemplifies one of the fundamental values of our group: Solidarity.

Malaria

The disease

Malaria is a parasitic disease, transmitted among humans via the intermediary of the Anopheles mosquito. Malaria causes attacks of fever and various other disorders. The parasite, known as *Plasmodium*, colonizes and destroys red blood cells. It is the destruction of the latter that leads to malaria attacks, the symptoms of which are: sudden appearance of fever, fatigue, headaches, shivering, vomiting, etc. Attacks can sometimes become severe, leading to serious anemia, convulsions, coma, and even death. Young children and pregnant women are particularly at risk of developing severe malaria.

Epidemiology

Malaria is the most widespread transmissible disease, affecting most tropical and sub-tropical countries of sub-Saharan Africa, South and South-East Asia, and certain parts of South America. An estimated one-third of the world's population lives in malaria-affected areas. Every year approximately 500 million people will suffer an attack of malaria, and 1 to 2 million people will die from it. More than half of the deaths will be children under the age of five.

Malaria is a poverty-related disease, for two reasons:

- Poverty fuels malaria because the disease develops wherever there are Anopheles mosquitoes, non-controlled sources of fresh water where the insects breed and Plasmodia-carrying patients who perpetuate the disease transmission. These conditions, which have now been eliminated from formerly malaria-infested countries such as the United States or Australia, are to be found in many developing tropical countries.
- Malaria fuels poverty because of the expenses and losses that it entails (in many sub-Saharan African countries, malaria is the largest single health-expenditure item) and because of its impact on sufferers' ability to work and receive an education.

Impact Malaria Program
ww.impact-malaria.com

Anopheles mosquito, main vector of malaria

Treatments and strategies for combating malaria

Treatment of non-complicated malaria is these days based on a combination of drugs, which always include an artemisinin-derivative and another antimalarial medicine (Artemisinin-based Combination Therapy, ACT) (Source: Guidelines OMS, 2006). Artemisinin comes from the Artemisia plant *(Artemisia annua)*, the antimalarial properties of which became clear in China in the 1970s - 1980s. The aim of combining two antimalarial treatments is essentially to overcome the parasite's ability to build up a resistance to one of the two drugs. **Severe (or complicated) malaria** is mainly treated with quinine injections.

The fight against malaria, however, goes beyond treating attacks with effective, high-quality medicines. It also includes preventing bites from the carrier mosquitoes. This can be achieved using mosquito nets impregnated with insecticides (especially for children under five and pregnant women).

An effective, sustainable antimalarial strategy must include the mobilization of human and material resources aimed at conducting various simultaneous tasks:

- diagnosis of malaria cases;
- effective and safe treatment, accessible to all patients;
- combating the mosquitoes (Anopheles), including,
  - entomological studies so as to better understand the characteristics of the Anopheles mosquito in each affected area,
  - mosquito nets impregnated with insecticides,
  - indoor and outdoor insecticide spraying,
  - destruction of larval habitats,
  - community awareness-raising about malaria prevention and care for malaria sufferers,
  - establishment of epidemiological and medical data monitoring (concerning the number of malaria cases, movement of Anopheles mosquitoes, etc) so as to optimize use of human and material resources.

This approach to fighting malaria - the « comprehensive fight » - relies on political will to mobilize the necessary resources and appropriate funding. Special awareness-raising among governments and all major international stakeholders is currently underway. Considerable sums of money are becoming available thanks to initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Bill and Melinda Gates Foundation, UNITAID, and many other national and international initiatives, in both the public and private sectors.

The sanofi-aventis advantage

Sanofi-aventis has been present in Africa for decades, and, more extensively, in countries affected by malaria, thanks to its affiliates, offices and manufacturing facilities. Our portfolio of products contains several antimalarial drugs, including certain medicines that helped lay the foundations of treatments for the disease (quinine, chloroquine, amodiaquine), more recently artesunate and artemether, and today the artesunate-amodiaquine combination. In July 2001, the Impact Malaria initiative, the first program from the « Access to Medicines » team, was created. It aims to mobilize the company's expertise and resources to join the fight against malaria.

The sanofi-aventis initiatives

The Impact Malaria activities are organized around **4 priorities**: research and development of new antimalarial drugs, the development of new formulations and combinations using current drugs, training and information at all levels of the health-care process, and implementing a pricing and distribution policy suited to promoting better access to treatments. These activities are carried out with the close cooperation and active support of many partners in countries where the disease is endemic.

Priority 1

Research and development of new antimalarial drugs

We know that the parasite responsible for malaria is able to rapidly develop resistance to all treatments. For this reason, there is a constant need for new compounds. This is a race against time, and we must stay ahead of new resistant strains. Such is the objective of research programs, undertaken in partnership with university laboratories, then developed in our own research centers and wholly financed by the sanofi-aventis Group. Collaborative research with Montpellier II University (Pr. H Vial) was begun in 2003 on a series of products called « bicationic compounds » that interfere with phospholipid biosynthesis in the parasite, which led to the selection of a candidate for development: SAR97276.
Cooperation with Palumed in Toulouse (Dr. B. Meunier) on « trioxaquins », compounds potentially associating two action mechanisms against the parasite started in 2002.
Finally, ferroquine, or SAR97193, a new 4-aminoquinoline derivative, the result of cooperation with USTL (Lille, Pr. Brocard) begun in 2002. Ferroquine is very effective against strains of *Plasmodium falciparum*, whether they are sensitive or resistant to chloroquine. It is currently undergoing clinical trials.

Priority 2

Development of new formulations and combinations using current drugs

Combination therapy: overcoming increasing resistance

Faced with the worrying emergence of resistant parasites, since 2004, the WHO has been recommending first-line treatment associating two antimalarial compounds, one of which must be an artemisinin derivative (ACT: *Artemisinin-based Combination Therapy*).
To respond as rapidly as possible to this requirement, sanofi-aventis, which had oral administration forms of amodiaquine and artesunate at its disposal, developed treatments composed of the two modified antimalarial compounds in the same thermally molded pack: the co-blister format. The artesunate-amodiaquine co-blister, produced in one of the Group's plants in Morocco, has been on the market for the last few years in more than 20 African countries.

An alternative to administration of quinine salts by injection

The treatment of severe malaria in children requires the parenteral administration of quinine salts as early as possible after the appearance of the first clinical signs. If left untreated, or if treatment is delayed, the disease can be fatal. In isolated rural areas, parenteral administration is very uncertain (lack of material, risk of infection, etc.). Confronted with this situation, sanofi-aventis is developing a pediatric emergency kit for the intra-rectal administration of quinine, while awaiting transfer to a properly equipped healthcare structure.

Several field studies have been conducted to determine the best place for the emergency kit in real life situations.

For simpler use of the emergency kit, a ready-to-use pre-diluted solution of the medicine should be available in 2007.

The artesunate-amodiaquine fixed-dose combination: Market approval in sub-Saharan Africa in 2007.

To further improve patient treatment compliance, a set combination, combining two antimalarial drugs in a single tablet has been developed: the artesunate-amiodiaquine fixed-dose combination. This development was undertaken in partnership with DNDi (Drugs for Neglected Diseases initiative) which coordinated the process of perfecting the artesunate-amiodiaquine co-formulation. Through its agreement with DNDi, sanofi-aventis relinquishes its right to any patent and is committed to supplying this new antimalarial treatment at prices scaled to the incomes of the populations concerned, in particular for the most vulnerable. In this partnership, each party is pouring its expertise and resources into a shared project.

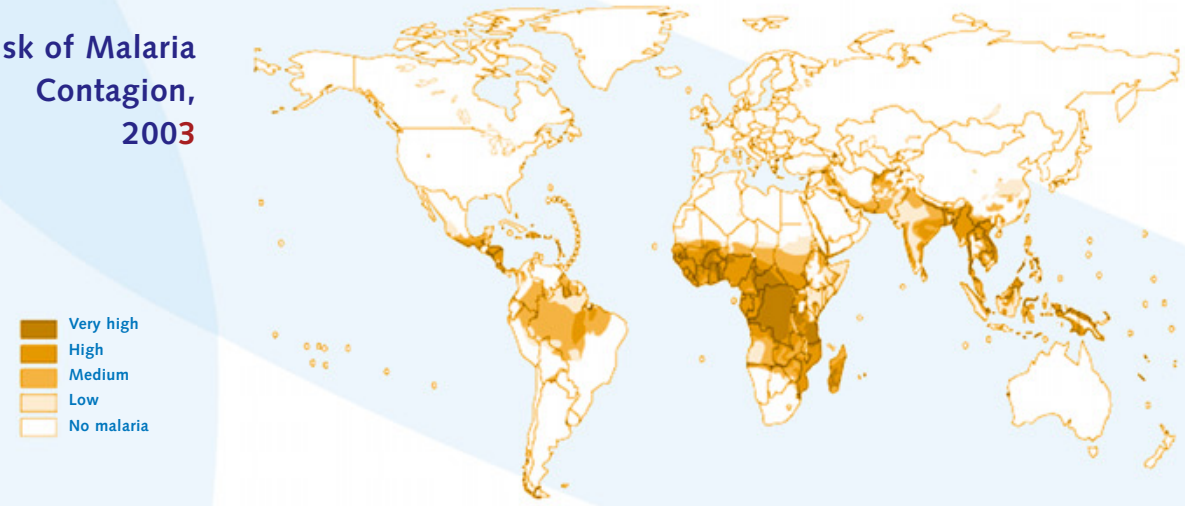
This medicine, produced in Morocco, received official market approval on February 1, 2007, and is to be registered in most sub-Saharan African countries in 2007-2008.

African countries' adoption of ACTs, a process already under way

2005

Source: RBM-AFRO

Risk of Malaria Contagion, 2003



Source: Hay SI, Guerra CA, Snow RW. Determination of country populations at malaria risk of different endemicities: report on agreement to perform work (APW) for WHO/Roll Back Malaria. Oxford, Oxford University, Department of Zoology, TALA Research Group, August 2004 (M50/370/19).

Priority 3

Information, Education and Communication

Drugs alone are not enough. Care needs to be taken to ensure that they are used correctly. The Impact Malaria program includes Information, Education and Communication (IEC) initiatives aimed at everyone involved in the fight against malaria.

I - Initiatives aimed at medical staff

These aim to disseminate information as to the most up-to-date recommendations regarding the diagnosis and treatment of malaria. These activities, tailored to suit each country, are conducted in partnership with national antimalarial programs. In so doing, sanofi-aventis offers health ministers ACT training tools, designed for healthcare practitioners.

To ensure the widest possible dissemination of current knowledge, Impact Malaria has also published a manual for prescribing physicians in endemic zones entitled « PaluTrop, » written by the best African and French specialists in the treatment of malaria. This 40-page educational manual is for prescribing physicians and nurses who find themselves working far from hospitals in their countries.

Thanks to Impact Malaria funding, the Army Medical Corps Institute of Tropical Medicine in Marseilles (IMTSSA) has provided certificate courses in malaria treatment for 60 African physicians.

Also in partnership with IMTSSA, as well as with the « Liverpool School of Tropical Medicine », the internet website www.impact-malaria.com has been developed, a communication and continuing education tool for everyone involved in the fight against malaria.

II - Initiatives aimed at local populations and communities

Impact Malaria develops and supports Information and Education initiatives for local populations regarding malaria prevention and correct usage of malaria treatments.

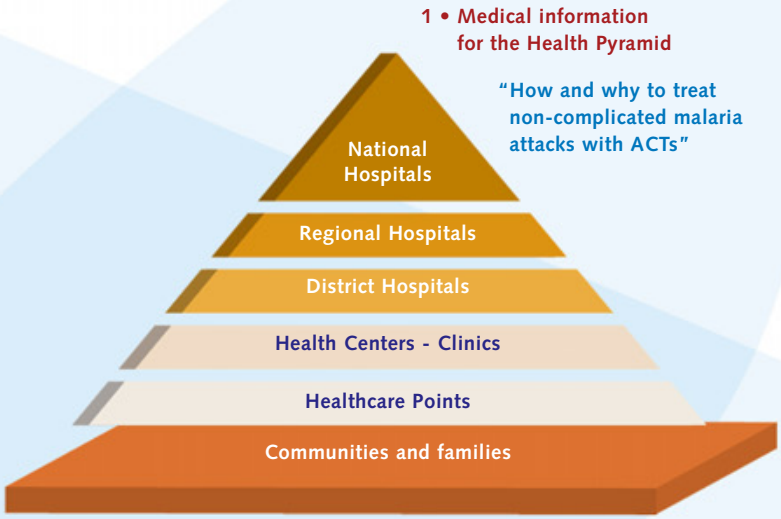
One example is the Pilot Project, carried out in partnership with CARE Cameroon, to combat malaria in the Lagdo region (Cameroon), an area which has a high prevalence of malaria because of its nearby lake, river and rice fields. As part of the project, surveys were conducted to see how malaria is viewed by local communities. These surveys meant that appropriate malaria prevention communication tools could be designed, tailored for use by the community as well as in health centers and schools in the area. The aim is to raise awareness among the community and the families of children under five who are particularly at risk of malaria-related complications. An entomological study has enabled better understanding of the Anopheles mosquitoes' behavior in the Lagdo region, facilitating the fight against the vectors of the disease. Finally, sanofi-aventis is to provide ACTs for treating confirmed cases of malaria.

Another project currently being prepared concerns the Makoua region in Congo Brazzaville, in partnership with the NGO, *Actions de Solidarité Internationales* (ASI) and the *Agence pour la Médecine Préventive* (AMP). Thanks to these projects, it will be possible to determine, for various regions with varying malaria transmission profiles, the resources that need to be mobilized in order to make a significant and lasting impact on the disease.

In Benin, the project conducted with PlanetFinance, run in partnership with NGOs which are established in the field, aims to train the educators among healthcare professionals, so as to raise awareness of malaria risks in families and communities. Malaria prevention and disease symptom information kits, using pictograms that can be understood by everyone, including the illiterate, have been developed thanks to this partnership.

This experience has been most useful in countries where malaria is endemic when it comes to drafting plans for a comprehensive plan of attack and to obtaining the necessary funding.

Finally, sanofi-aventis has supported, along with Total and CFAO, the creation of a Practical Guidebook for the Corporate Fight against Malaria, which is now available. This Guidebook is made up of thematic sheets, and is designed to be used as a reference tool for firms wishing to organize malaria care for employees and their families and, beyond that, for the communities where the companies are located.



Priority 4

Implementation of a pricing and distribution policy for antimalarial drugs

So as to ensure the accessibility of our antimalarial drugs to the broadest possible number of patients, we have established a policy of differentiated prices.

The lowest price level is based on an optimization of production costs, without compromising on the quality of the product, which is identical for all production units, throughout the world. It is a price that enables the product to be sold without profit, but without any financial loss either, and is reserved for the most underprivileged. This approach is vital if the viability of production is to be guaranteed in the long term.

The main channels of medicines distribution for the countries affected by malaria are:

- private-sector pharmacies:
  sanofi-aventis offers the same antimalarial medicines at two different prices, tailored to patients' financial means:
  - the « princeps » drug, under the sanofi-aventis brand name, is available at a normal price for the country in question,
  - the same drug, under the Impact Malaria brand name, is available at a preferential price for the needy through the CAP Program (Antimalarial Drug Access Card Program). The CAP card is provided by the pharmacist to families whose income is below the poverty line for the country. It enables the family to purchase the medicine at a very accessible price. This has been made possible thanks to the commitment of wholesalers and pharmacists who have also renounced their profit margins.

- public health systems:
  The supply of antimalarial drugs in countries where the disease is endemic are made through invitations to tenders organized by purchasing groups, NGOs and United Nations organizations… As part of these calls to tender, sanofi-aventis offers its ACTs at the lowest possible price. The drugs are then distributed by the public health systems to hospitals, clinics, health centers, etc.

In 2005-2006 sanofi-aventis distributed more than 10 million ACT treatments at preferential prices in 16 afflicted countries.

With its plant in Casablanca, Morocco, the Group has a high-quality industrial tool that enables it to respond quickly to increased demand for ACTs with the artesunate-amodiaquine fixed combination.

Participation of private pharmacies in providing access to antimalarial drugs:

The Antimalarial Drug Card Access Program (CAP)

The program has been operating since 2004, in urban areas, in five countries:

- Gabon: pilot launch in Libreville in November 2004, extension to four other towns in May 2006.
- Madagascar: pilot launch in three large coastal towns in November 2004.
- Kenya: pilot launch in progress in 13 towns distributed throughout the country's provinces (February 2006).
- Mali: pilot launch in progress in the six municipal districts of Bamako (March 2006).
- Congo-Brazzaville: simultaneous pilot launch in Brazzaville and Pointe-Noire (May 2006).

Participants in the program: nearly 400 of the 650 pharmacies in the areas concerned.

Results: in two years, over 26,000 families have benefited from the Impact Malaria card, via 400 private pharmacies, enabling nearly 47,000 patients to receive antimalarial drugs at a preferential price.

A step further: the CAP club

The CAP club was launched in June 2006 at the International Pharmaceutical Forum in Brazzaville.

Participants: member pharmacists and CAP program partners.

Objectives: information exchange, media coverage, and promotion of social activities to combat malaria carried out by pharmacists and by those active in the CAP program.

Through these four priorities, Impact Malaria establishes short-, medium- and long-term activities that are designed to make a lasting impact. We are focusing on the very « heart » of our vocation, which is to develop, register, produce and market high quality medicines at prices that are within everyone's reach. However, based on the observation that medicines alone cannot solve all problems, Impact Malaria is also involved in Education, Information and Prevention initiatives by promoting the principle of the « comprehensive fight » against malaria.
Thanks to the involvement of its many partners who support Impact Malaria, both in-house and external, sanofi-aventis is truly a major player in the fight against malaria.

Tuberculosis

The disease

Koch's bacillus *(Mycobacterium tuberculosis)*, which causes tuberculosis, is an infectious agent transmitted by breathing in airborne droplets expectorated by infected patients. The inhalation of a few contaminated droplets is sufficient to infect a person. The bacteria usually leads to infection of the lungs, but sometimes other organs are affected too (bones, the meninges, lymph glands).
A person with untreated tuberculosis can infect an average of 10 to 15 people every year. Population movements (travelers, war refugees, the homeless in industrialized countries) have greatly contributed to the global spread of the disease in the last 40 years.

Not all people infected with Koch's bacillus will develop the disease. The bacillus can remain dormant in the body for years without symptoms. Only 5% to 10% of those infected will develop tuberculosis. Immuno-suppressed people, particularly patients with HIV/AIDS, have a greater risk of developing tuberculosis after being infected.
Together the HIV virus and Koch's bacillus are a fatal mix, with each infectious agent promoting the progression of the other. Tuberculosis is the main cause of death in patients with HIV/AIDS; this disease is responsible for the death of a third of these patients worldwide and 40% of the deaths among HIV/AIDS patients in Africa.

Epidemiology

Tuberculosis is, along with HIV/AIDS and malaria, one of the most serious infectious diseases at large in the world. Today, one third of the world's population is infected. It has been estimated that every second someone in the world is infected with Koch's bacillus, and that every year around 8 million people will develop the disease and 2 million people will die from it.

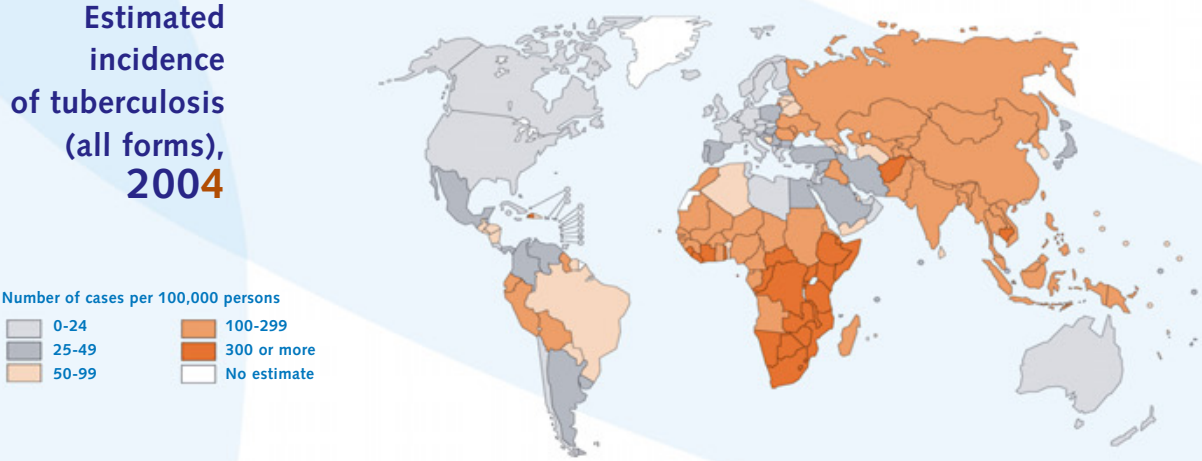
Twenty-two countries alone account for 80% of tuberculosis cases worldwide.
Over 2 million of the annual cases occur in Sub-Saharan Africa, a figure which is rapidly increasing due to the HIV/AIDS epidemic which also particularly affects the region. Nearly 3 million of the annual cases of tuberculosis are registered in South-East Asia, and over 250,000 are in Eastern Europe.

The HIV/AIDS epidemic and the emergence of bacilli that are multi-resistant to antibiotics help exacerbate the impact of the disease, considered by the WHO to be a global health emergency.
The WHO estimates that between 2000 and 2020, nearly a billion new people will be infected, of which 200 million will develop the disease, and 35 million will die if there is no improvement in handling the infection.

Treatments and strategies for combating tuberculosis

The aim of curative treatment is to destroy the bacteria present in the infected organs. It is based on a combination of four antibiotics: rifampicin, isoniazid, pyrazinamide and ethambutol. This is the standard treatment currently recommended by the WHO. It must be started as early as possible and must be followed for at least six months.
The WHO considers that, from the public health standpoint, incomplete treatment or poor compliance is worse than no treatment at all.
Indeed, if the infection is not eliminated, it can lead to the appearance of antibiotic-resistant bacilli in the patient. Treating resistant bacilli, when it is possible at all, takes a lot longer, is more complicated and more expensive.

Estimated incidence of tuberculosis (all forms), 2004



Source: The global plan to stop TB 2006-2015 - Stop TB Partnership - WHO.

Educational DOTS illustration in South Africa

These people spread drug-resistant strains of bacteria and are contributing to the emergence, already particularly worrying, of multi-resistant bacilli.

So as to ensure correct adherence to first-line treatment, fixed-dose combinations (or FDCs) have been developed. The four main drugs of the initial two-month phase of treatment are rolled into one single tablet, or the two main drugs for the following phase of at least four months' duration, and considerably reduce the number of tablets to be taken each day.

Patient supervision and monitoring throughout the treatment also ensures better treatment compliance.

At international level, the recommended weapon to effectively combat tuberculosis is « DOTS » or *Directly Observed Treatment Short-course* strategy.
DOTS refers to the close monitoring of daily administration of medication by a person other than the patient, known as a « DOTS supporter ».

After diagnosing cases of tuberculosis, healthcare personnel, community care workers or volunteers with the required training supervise the patients directly to make sure they take the prescribed dose of antituberculosis drugs for the entire duration of the treatment.

After two months of treatment, and again at the end of the treatment, a new sputum examination is performed to ensure that tuberculosis has been cured.
The patient registration and disease notification system permits surveillance of disease's development throughout the entire treatment. It also means that assessments can be made of the proportion of patients cured, thus providing a program quality indicator.

If correctly applied, this strategy could avoid millions of cases and deaths in the coming decade.

The sanofi-aventis advantage

Historically, sanofi-aventis was the very first company to manufacture rifampicin and remains one of the main producers of this fundamental ingredient in all antituberculosis treatments. Several of the Group's manufacturing facilities have developed and currently produce a complete range of antituberculosis agents, distributed in many countries. Building on the strength of this experience, sanofi-aventis recently redefined its contribution to the fight against tuberculosis.
A program of optimization and industrial development has begun, so that the product range can be extended and so offer better-adapted products at the lowest prices, improving access to treatment for a greater number of patients.

Inauguration, in the presence of Jean-François Dehecq, of the 1st DOTS centre - South Africa, 2005

This program essentially relies on existing capacities in South Africa, including the Waltloo industrial site, which will ultimately produce all of the Group's antituberculosis drugs.

Sanofi-aventis is already providing patients with a fixed association of the four drugs for the first stage of treatment and two drugs for the subsequent phase.

The goal of the tuberculosis program is to offer health authorities in the affected countries a range of high-quality antituberculosis products, as well as tailored support initiatives, as part of the fight against the disease.

The sanofi-aventis initiatives

Sanofi-aventis has established, in partnership with numerous international organizations, such as the CDC (Center for Disease Control and Prevention) in the United States, TB Alliance, CREATE (Consortium to Respond Effectively to the AIDS/TB Epidemic), St George's Hospital Medical School London, etc, a strategy for developing and improving tuberculosis treatment, based on:

- continued development of an existing drug, rifapentin, in the treatment of latent and active tuberculosis, both alone and in combination with other drugs. The aim is to shorten treatment duration and reduce the number of times that medication has to be taken, while nevertheless maintaining optimal effectiveness,
- systematic screening of its portfolio of antibiotics so as to identify new products that may be effective against the tuberculosis bacillus, especially the kinds that have developed resistance to standard treatment,
- research on new drugs, possibly with recourse to external partners.

This new sanofi-aventis research and development program is in step with the aims of STOP TB, a world-wide program under the auspices of the WHO and the United Nations « Millennium Summit » objectives, which are essentially to curb the spread of tuberculosis and thus reverse its incidence as of 2015.

The TB Free Program

With nearly 400,000 new cases annually and an average of 175 deaths daily, South Africa is among the countries most affected by tuberculosis.

The TB Free Program that has been implemented in South Africa was developed in partnership with sanofi-aventis, the Nelson Mandela Foundation and the South African Health Department. It aims to help raise awareness about the disease, the importance of diagnosis as soon as the first symptoms appear, and support for tuberculosis patients - DOTS supporters - whose task is to directly supervise patient treatment compliance.

The goal is to open nine new centers (one per region), and to ultimately train over 20,000 DOTS supporters nationwide, each monitoring about ten patients throughout their treatment.

Tsetse fly, main vector of sleeping sickness

Sleeping Sickness

or Human African Trypanosomiasis (HAT)

The disease

HAT is a poverty-related disease, complex and deadly.

HAT, or **sleeping sickness**, is one of the most complex - and one of the most neglected - of all endemic tropical diseases. Transmitted by the bite of the tsetse fly, this illness is rife mostly in Western and Central Africa, while the Rhodesian variety of the disease can be found in East Africa.

Sleeping sickness is a disease for which the effectiveness and innocuousness of the treatment depends on proactive screening so that cases are diagnosed early. During the initial phase of the illness, when treatment is well-tolerated and offers a high probability of a cure, the symptoms are generally minor and non-specific. This is why many patients do not seek medical advice until they are in too advanced a stage of the disease, by which time the parasite has already invaded the brain. Neurological problems then become too severe, including the disturbed sleeping patterns, hence the disease's name.
The disease rapidly develops toward an irreversible coma, leading to the inevitable death of the patient. Treatment of this neurological phase (stage two of the illness) is thus more complex, dangerous and without guaranteed results.

If left untreated, the disease is long, painful and always fatal.

Epidemiology

In 1995, the WHO estimated that some 300,000 people were afflicted with the disease (Reference: WHO Series of Technical Reports N°881). In its 2001 report **(WHO/CDS/CSR/ISR/2000.1 WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases)**, the WHO set the figure of people at risk of infection at 60 million, out of whom only 4 to 5 million had access to any kind of monitoring.

In 2006, the WHO estimated the number of cases to be 70,000. This improvement is the result of the WHO's mobilization, as well as that of national programs and NGOs. It was largely thanks to the major contribution made by sanofi-aventis since 2001, outlined in the upcoming pages, that made the WHO's central role possible.

The motivation behind our commitment 2001-2006

In 2001, Aventis (now sanofi-aventis) was the manufacturer of the main medicines that are effective against sleeping sickness (pentamidine, melarsoprol and eflornithine):

- With pentamidine (200 mg) in intramuscular (IM) injection in the first phase of the disease.
- With melarsoprol and eflornithine in intravenous (IV) injection in the second phase of the disease.

At that time, Aventis recognized that for such a complex disease, medicines alone, while indispensable, would not be enough to win the battle against this illness, and so signed an agreement with the WHO (May 2001) in which the Group pledged 25 million dollars over a period of five years to:

- Produce the medicines and supply them in quantities sufficient to cover treatment needs.
- Support WHO activities to strengthen monitoring programs and programs combating the disease in accordance with epidemiological developments.
- Support the WHO so as to oversee the drugs' passage from producer to patient.
- Support WHO efforts to stimulate research and development activities for new monitoring tools.

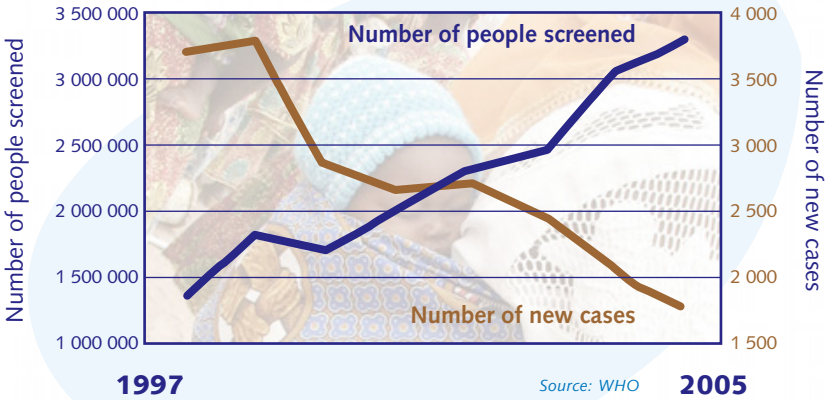
Lumbar punction, HAT diagnosis

The results

Thanks to this initial partnership, between 2001 and 2006, more than 320,000 vials of pentamidine, over 420,000 vials of melarsoprol and over 200,000 bottles of eflornithine, produced by sanofi-aventis and given to the WHO, have been distributed to countries where the disease is endemic, thanks to the logistics of the association Doctors Without Borders (known as MSF - *Médecins sans Frontières*).

The financial contribution, supplementing the donation of drugs, helped bolster national anti-HAT programs. Over 300 people (field staff) were trained by the WHO. The staffing reinforcements, as well as the technical and financial support for anti-HAT activities, meant that there has been a significant increase in the number of people screened and treated.
In this way, nearly 14 million diagnoses have been made during the five years of the partnership. This has thus greatly contributed to stemming the spread of sleeping sickness, to saving nearly 110,000 lives and to changing the epidemiological profile of the disease, meaning that eliminating it altogether can now be envisaged.

Number of people undergoing proactive screening and number of new Human African Trypanosomiasis cases recorded, 1997-2005



These results have enabled the International Scientific Council for Trypanosomiasis Research and Control to recommend that the WHO, during its 28th Conference in Addis Abeba (September 2005), launch a program to eliminate sleeping sickness, given that it is a serious public health issue, in the belief that this was an objective that was indeed conceivable.

(References: sanofi-aventis press communiqué, 10/10/06).

New cooperation between the WHO and sanofi-aventis 2006-2011

The next steps 2006-2011

The positive results of the 2001-2006 partnership between sanofi-aventis and the WHO in the fight against sleeping sickness have motivated and justified the decision taken by the sanofi-aventis Group's senior management to continue supporting WHO activities, which was signed into a contract on October 10, 2006.
Given its experience and all that was learned from the first partnership, sanofi-aventis will continue, for another five years, to support efforts to combat sleeping sickness and will broaden this support to other neglected tropical diseases such as leishmaniasis, Buruli ulcer and Chagas disease (Human American Trypanosomiasis).

This partnership, and the sum of 20 million euros (25 million dollars) that have been allocated to it, will make it possible to support WHO policy, which aims to better integrate activities that fight neglected tropical diseases, by maintaining and/or developing training programs as well as maintaining support for screening and treatment aspects of national action programs.

Signature of the new agreement, October 10, 2006, between J.F. Dehecq, Chairman-CEO of sanofi-aventis, and Dr A. Nordström, Acting Director-General, World Health Organization

Photo source: WHO - October, 2006

Leishmaniasis

The disease

« Leishmaniasis is a parasitic disease transmitted by the bite of the sandfly. This extremely complex disease has six forms. **Visceral leishmaniasis** (VL), which attacks the internal organs, is the most severe form. Left untreated, it is usually fatal within two years. Furthermore, a percentage of cases can evolve to skin dissemination of parasites **(post-kala azar dermal leishmaniasis)**. The **cutaneous form** is the most common. It usually causes ulcers on the face, arms, and legs. Although the ulcers heal spontaneously, they cause serious disability and leave severe and permanently disfiguring scars. Far more devastating is the **mucocutaneous form**, which invades the mucous membranes of the upper respiratory tract, causing gross mutilation as it destroys the soft tissues of the nose, mouth, and throat. **Diffuse cutaneous leishmaniasis** produces chronic skin lesions that never heal spontaneously, and finally, **recurrent cutaneous leishmaniasis** is a relapsing form which appears after treatment ».

(Reference: brochure on the new cooperation between the WHO and sanofi-aventis 2006-2011).

Epidemiology

Leishmaniasis is endemic in 88 countries on four continents: Africa, America (Central and South), Asia and Europe.
According to the WHO, some 350 million people are at risk of developing the disease. The Organization estimates that 12 million are currently afflicted, and that they live mainly in poor, isolated areas. Leishmaniasis affects about 1.5 to 2 million people every year. The disease causes thousands of deaths (70% of the victims are children) and leaves thousands more with severe disabilities.

Five hundred thousand people (about 25% of all new cases) contract the visceral form (fatal if left untreated) in 62 countries. Every year, more than 50,000 people die from VL.
The vast majority (90%) of kala azar sufferers live chiefly in Bangladesh, Brazil, India, Nepal and Sudan.

1.5 million people (75% of all new cases) contract the cutaneous form of the disease. The vast majority (90%) of these patients live in the following six countries: Afghanistan, Algeria, Saudi Arabia, Brazil, Iran, Peru, Sudan and Syria.

Ninety per cent of all mucocutaneous leishmaniasis cases are found in just three countries: Bolivia, Brazil and Peru.

Treatments and strategies for combating leishmaniasis

There is currently no vaccine or prophylactic medication available. The only individual preventive measures that are effective to date against the disease are: insecticide-impregnated mosquito nets and the use of insecticides such as DDT. Additionally, care must be taken to screen and monitor animal reservoirs (dogs and small forest rodents).
Treatment of the disease is based on pentavalent antimony (meglumine antimoniate and sodium stibogluconate), still today considered to be the first-line treatment, and on the second-line drugs, namely amphotericin B, liposomal amphotericine B, pentamidine isethionate, paromomycin and miltefosine.

Sanofi-aventis markets meglumine antimoniate and pentamidine, which are considered by the WHO to be essential drugs in first-line and second-line treatments, respectively, for all forms of leishmaniasis.

Given the large number of people affected by the disease in certain countries and the high prices of these different treatments, the cost of controlling this scourge would weigh extremely heavily on the countries' health budgets.
This is one of the reasons why sanofi-aventis decided to take its commitment even further.

The sanofi-aventis project in the fight against leishmaniasis

This project comprises two initiatives:

- A sanofi-aventis supply of meglumine antimoniate at a preferential price
- A partnership with the WHO designed to improve control of the disease.

Meglumine antimoniate is produced and distributed by sanofi-aventis in many countries. To make the product available to the greatest number of patients, rationalization of production was started in 2005, aiming to limit production of all the treatments to one single production site. Eventually, world production for this drug will be concentrated on a single site in Suzano, Brazil. As a result, we will be able to distribute the drug using a tier-pricing policy providing better access to treatment for a greater number of patients worldwide.

As part of the new five-year partnership signed on October 10, 2006 with the WHO, 25% of the sanofi-aventis donation (6.4 million dollars) will be earmarked for combating leishmaniasis.

Sanofi-aventis' aim is to be active in the struggle against this neglected disease, through a two-pronged initiative: Information, Education and Communication with the WHO, but also through the activities of some of the Group's affiliates, acting in concert with national authorities (for example, in Latin America).

Epilepsy

The disease

Epilepsy is an organic neurological disorder, caused by the abnormal function of nervous brain cells, or neurons. This muddled functioning of the cells, caused by excessive, sudden electric discharges, manifests as a seizure. An epileptic seizure describes clinical manifestations whose unexpected, sudden onset is linked to the dysfunction of a portion, or all, of the neurons in the cerebral cortex. Seizures are always sudden and usually short-lived. They can vary depending on the area in the brain where the discharges occur.
Two kinds of seizures can be identified:

- seizures of the entire body, involving both cerebral hemispheres. During this type of seizure the patient usually loses consciousness suddenly, falls and experiences convulsions, sometimes violent in nature. The patient is at risk of suffering injuries during the fall. The seizure usually lasts one to two minutes, but may sometimes be only a few seconds long.
- partial or localized seizures, which are the result of abnormal activity in one part of the brain. Only part of the body is affected, or the seizure may also manifest as memory or consciousness disorders.

Having a seizure does not necessarily mean that one is epileptic. It is considered to be Epilepsy when the seizures are recurrent, occurring relatively frequently and for a more or less sustained period in the life of the individual.
Epilepsy may be caused by a cerebral event stemming from a trauma, genetic predisposition, cerebral lesions due to birth complications, infections, cerebral vascular accident, metabolic disorders, etc. However, in more than half of all cases, the cause of the Epilepsy is unknown. Epilepsy rarely runs in families.

Epidemiology

Epilepsy is the most widespread neurological disorder in the world, aside from migraines. It runs across geographical, ethnic and social borders. Throughout the world, about 5% of the population will suffer a seizure at some point during their lifetime and 0.5% to 1% will be Epilepsy sufferers.

Epilepsy affects over 50 million people worldwide, 85% of whom live in developing countries, where the disease is more prevalent.
In developing countries, the incidence of the disease is from 49 to 190 new cases annually per 100,000 inhabitants, with incidence peaking at either end of the age scale.
In some societies, the convulsive fits are considered to be the result of possession by evil spirits. Patients are thus sent to healers or exorcists instead of a doctor, and, as they are neither diagnosed, nor treated, they live on the margins of society.
The vast majority of children and adults diagnosed with Epilepsy can be successfully treated with currently available medicines. But most epileptic patients in developing countries (80%) are not currently receiving treatment, and are sometimes not even diagnosed due to lack of access to healthcare structures and the medicines which could treat them. This has serious physical, psychological, social and economic consequences for patients and their families.

(Reference: WHO, "Atlas-Epilepsy Care in the world 2005")

The sanofi-aventis advantage

The sanofi-aventis Group produces two of the world's most-used treatments for Epilepsy, with phenobarbital, which has been available on the market for over sixty years, and sodium valproate, which revolutionized the way in which epilepsy was treated, and therefore the lives of millions of epileptics throughout the world, nearly forty years ago.

Phenobarbital and sodium valproate are on the WHO list of essential medicines and are part of the basic therapeutic arsenal used in the care of epileptic patients. It was no doubt on the strength of this immense legitimacy, as well as sanofi-aventis' deep involvement in the world of neurology through its numerous continuing education programs, that prompted Santé Sud, a new NGO from Marseilles, to contact the Group in 2004.

Santé Sud is a medical development NGO intervening in the poorest countries. It has assisted with the development of a training and installation program for general practitioners whose aim is to extend medical care to the most isolated rural regions of Mali.

As there was no national program for the treatment of epilepsy in rural areas, Santé Sud, together with the « Association des Médecins de Campagne » (Association of Country Doctors), decided to launch a program. Six general practitioners were then trained and organized into a network called RARE (a French acronym for « Epilepsy Research Action Network »). With the assistance of Santé Sud, French volunteer neurologists and sanofi-aventis, these doctors now treat over 1000 epileptic patients, some of whom receive sodium valproate (200 mg and 500 mg), sold at a preferential « no profit-no loss » price.

Our commitment

The Group is determined to pursue this kind of initiative, in partnership with NGOs or university institutes, which guarantees quality training programs for all healthcare professionals, as a long-term commitment. It is also a way of ensuring that doctors have received the necessary information for optimizing prescription of the available antiepileptic treatments.
This determination is reflected in our recent agreements, made between sanofi-aventis and:

- The IENT (Institute of Epidemiology and Tropical Neurology) in Limoges, France, to enable the creation of the first Association against Epilepsy in Cambodia.
- Santé Sud, to renew the program under way in Mali for a further two years, and commence a similar kind of joint effort in Madagascar for three years.
- KAWE (Kenyan Association for the Welfare of Epileptics), to develop training programs already under way and facilitate access to antiepileptic drugs in Kenya.

Our commitment has enabled us to identify the conditions that are indispensable for better treatment of epileptic patients in rural areas:

- the presence of medical personnel is essential,
- further epilepsy-specific training required for the medical community,
- indispensable medicines must be made available with guaranteed quality and logistics, and at an affordable price for patients and their families.

In the light of the results of these initial pilot initiatives, sanofi-aventis hopes to extend its commitment in association with other involved partners.

Immunisation against polio with an oral vaccine

Vaccines

Through sanofi pasteur, sanofi-aventis is one of the foremost leaders in vaccine production. For several decades, sanofi pasteur and many partners have been involved in programs focused on providing the poorest countries with access to vaccines and ensuring that the vaccines are administered properly. This philosophy is fully integrated into sanofi pasteur's corporate strategy, which ensures its sustainability.

However, major differences do exist between the world of vaccines and that of pharmaceutical drugs. Whether in establishing objectives or in implementing them, the processes involved in access to vaccines differ substantially from those involved in access to medicines.

« Access to Vaccines » is much more complicated than « Access to Medicines »

Although immunization saves millions of lives worldwide, it is estimated that annually, 30 million newborn children miss out on vaccination and 3 million die from vaccine-preventable diseases. Access to vaccines is therefore a crucial issue, but it differs from Access to Medicines for three main reasons.

- Firstly, « access » is a relatively new concept in the pharmaceutical world, whereas it has long been integral to the world of vaccines.

- Secondly, given the small number of producers and the complexity of vaccine manufacturing processes, the worldwide vaccine demand can, at times, exceed the manufacturers' production capacity, which leads to shortfalls in the supply of some vaccines. This situation is non-existent in the pharmaceutical world where manufacturing processes are tailored to meet supply and demand fluctuations.

- Finally, it is absolutely essential to ensure that every stage of what is commonly called « the cold chain », in other words the long and complicated process of storing and distributing vaccines. Vaccines, since they are made from biological products, tend to be more unstable. Therefore, to maintain their quality, vaccines must be constantly stored under the appropriate temperature conditions.

« Access to vaccines » has been an issue for more than three decades

The issue of access to vaccines for the most underprivileged countries has been a concern for the international community since at least 1974, when the World Health Assembly established the Expanded Program on Immunization (EPI).

Along with other international vaccine companies, sanofi pasteur has been leading in the practice of « sliding-scale pricing » for a number of years. This system entails selling vaccines at a lower price to the poorer countries. Through the involvement of various stakeholders, immunizing a child against the 6 EPI diseases costs under US$30, with approximately 5% of that expense coming from the cost of the vaccines for the 6 EPI diseases.

Registration, manufacturing and distribution processes are fundamentally different from those of pharmaceutical drugs

There are significantly fewer vaccine producers than pharmaceutical drug manufacturers. Moreover, the vaccine market represents only 2% of the worldwide pharmaceutical market.

As with any biological product, each vaccine registration is based on its manufacturing process, which has several implications: the registration of « generic » vaccines is not possible as the entire manufacturing process and equipment have to be included in the application file for approval; any given vaccine must have one single producer; and each vaccine supplied via a United Nations agency has to be accepted, or « pre-approved », by the WHO. The complexity of this process explains why it takes approximately five years for a new industrial facility to start supplying vaccines to the marketplace. Vaccine production cycles are extremely long: 10 to 22 months, or even longer for more

complex vaccines. This further limits the speed at which manufacturers can respond to supply/demand fluctuations. In the current environment where vaccines are often perceived as inexpensive and minimally profitable, many manufacturers have discontinued their production. UNICEF used to rely, some years ago, on seven to eight producers for a given product, whereas only few remain today.

The GAVI partnership

Until the early 1990s, essentially the same vaccines were used worldwide, which meant that higher prices applied to wealthier countries, while the poorest countries could be supplied in a manner commensurate with their resources. Since then, vaccines calling for more complex technologies (acellular pertussis, conjugated pneumococcal and *Haemophilus influenzae* type-b vaccines) and combination vaccines have been developed. These new vaccines have resulted in significantly higher development and manufacturing costs. This has progressively led to the development of vaccine production that meets the needs and resources of wealthier countries but cannot be offered to the poorest countries at an acceptable price given their limited resources.

One of the main aims of the GAVI (*Global Alliance for Vaccines and Immunization*) initiative, founded in 2000 by the Bill & Melinda Gates Foundation, the World Bank, the WHO, UNICEF and vaccine manufacturers, is to limit the increasing discrepancy between wealthy and poor countries regarding access to the most innovative vaccines. Sanofi pasteur shares GAVI's vision to supply vaccines at an affordable price, improve the infrastructures required for proper vaccine administration and encourage research and development programs focused on diseases that predominantly affect developing countries.

Sanofi pasteur: a multi-level involvement

- **Supply vaccines to international organizations**

True to its founders and heritage, sanofi pasteur has long been an active proponent of access to vaccines for the poorest countries. For instance, in 2005, sanofi pasteur supplied UNICEF with over 400 million doses of vaccines.

GAVI: Global Alliance for Vaccines and Immunization

Polio - Sanofi pasteur is a partner with the WHO on the worldwide poliomyelitis eradication initiative. Over the years, sanofi pasteur has donated 120 million doses of vaccines to African countries. In 2005, sanofi pasteur supplied over 350 million doses of oral polio vaccines (OPV). In 2004-2005, sanofi pasteur produced and registered monovalent type-1 OPV vaccine in record time, which was requested by the WHO for the final stages of eradication in South Asia and Egypt.

Yellow fever - In the Northern Hemisphere, yellow fever vaccination is generally only used by travelers.

However, sanofi pasteur has developed a multi-dose formulation of this vaccine, specifically designed for extensive use in endemic countries. Sanofi pasteur is a major supplier of this vaccine for UNICEF and for a « stockpile », which serves as a backup reserve for a rapid emergency response to epidemics such as the one currently affecting Africa.

In order to assist countries in their efforts to organize yellow fever vaccination campaigns and prevent the appearance of epidemics, sanofi-aventis and sanofi pasteur support the *Agence pour la Médecine Préventive* (AMP) actions, such as the meeting organized by the AMP in partnership with the WHO in December 2006 in Bamako, Mali, regarding the use of yellow fever vaccine in Western African countries. At this meeting, which brought together 50 participants from eight West African countries, the involvement of sanofi-aventis and sanofi pasteur reflected their wish to not only supply vaccines, but also help ensure that the vaccines are used appropriately by those countries in need.

• **EPIVAC**

Supplying vaccines at affordable prices is essential. However, the major component of immunization-related expenses lies with factors other than the vaccine price. Vaccines must be stored and transported at the correct temperature from the point of manufacture all the way through to the individual being vaccinated. Vaccinations must be performed using proper aseptic techniques and at the proper ages according to local epidemiology. Training medical personnel to use vaccines properly is therefore crucial. Within the GAVI framework and with the support of the *Agence pour la Médecine Préventive* (AMP), sanofi pasteur is funding EPIVAC, a training program for public health field representatives working in West Africa. Over 195 people from 8 different countries have benefited from this « good vaccination practices » program since 2002. An inter-university diploma awarded by the Paris-Dauphine and Abidjan-Cocody universities validated their training.

• Epidemiological studies

The key to controlling vaccine-preventable diseases lies with an in-depth understanding of their epidemiology. Like all infectious diseases, these pathologies are complex as several components are involved: patients, pathogens (viruses, bacteria or parasites), sometimes vectors (e.g., mosquitoes) with always a human, animal or environmental reservoir to perpetuate the disease. It is crucial to understand where the burden of the disease lies, how it is transmitted, which age groups are affected, etc. if a suitable immunization strategy is to be established. Once immunization is introduced, it is also essential to document its impact and, if need be, adapt immunization strategies. To this end, sanofi pasteur is conducting numerous epidemiological studies, either directly or through external partnerships, for many diseases in which vaccines exist or will exist in the near future. Current efforts are focused on meningococcal meningitis in Africa, dengue fever in Asia and Latin America and influenza throughout the entire world.

• Research & Development

The sanofi pasteur Research and Development program also includes vaccines mainly or exclusively developed for the poorest countries. Sanofi pasteur is developing a vaccine against dengue fever, a mosquito-borne disease that plagues numerous countries worldwide and affects nearly 100 million people and causes 20,000 deaths each year, particularly in infants. Sanofi pasteur is also developing combination vaccines adapted to the needs of developing countries. Based on the hepatitis B vaccine produced in the Pilar plant in Argentina, these vaccines will enable immunization against five or six diseases in a single shot.

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