



Malaria

From the heart of Europe
to the Tropics

BUKO Pharma-Kampagne
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August-Bebel-Str. 62, 33602 Bielefeld, Germany

Fon +49-(0)521-60550,

Telefax +49-(0)521-63789

e-mail: pharma-brief@bukopharma.de

Homepage: www.bukopharma.de

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Text: Christiane Fischer, Claudia Jenkes, Jörg Schaaber
Christian Wagner-Ahlfs

Editor in chief: Christian Wagner-Ahlfs with Claudia Jenkes

Translation: Angela Mayr-Isenberg

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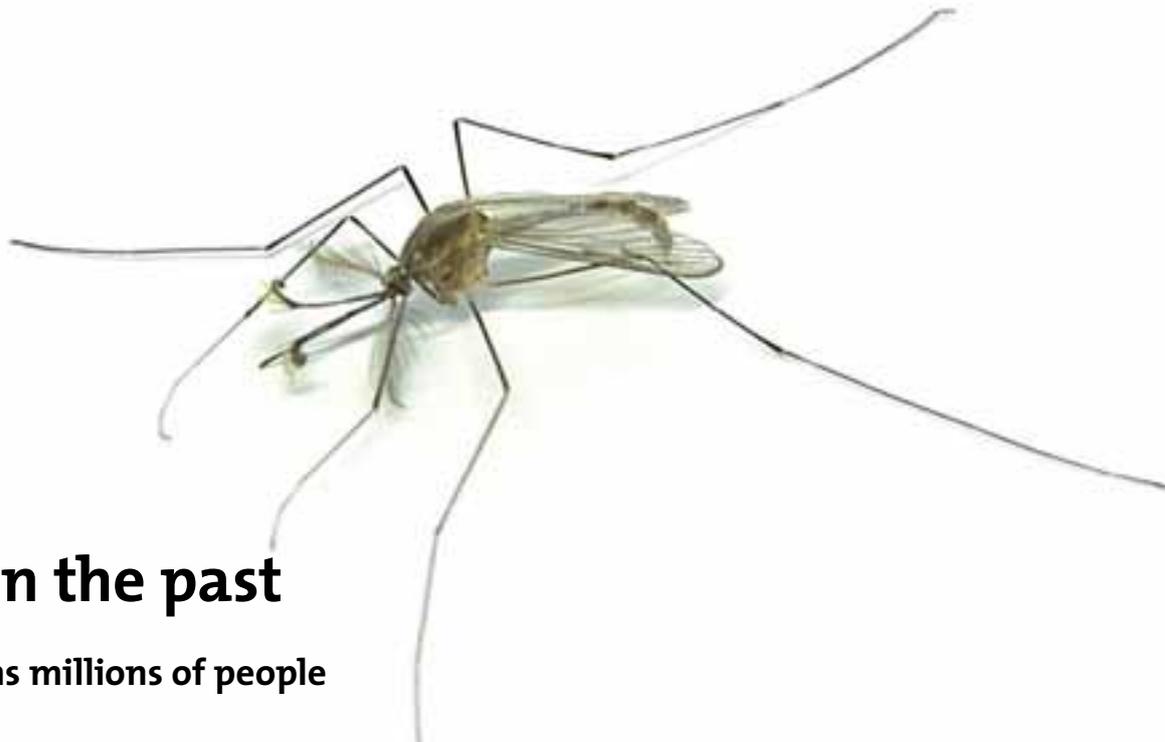
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asb.





Today as in the past

Malaria threatens millions of people

After the storm tides death took its massive toll. As though evil could come across the sea with the fumes and the sea fog, the coastal inhabitants crept away into their homes and avoided contact with the air outside. People believed that the brackish, putrid sea air brought the marsh fever.'

The marshes and moors in Northern Germany had been dreaded malaria regions up to the 19th century. During the epidemic in 1826, every second child is said to have come down with the marsh fever in East Friesland. Fortunately all that has long been gone. However, in the southern hemisphere, malaria still remains bitter reality. Almost one million people die of a fatal mosquito bite every year and every 30 seconds, a child dies. That is more than enough reason to have a look at the disease.

This Pharma-Brief Special provides basic knowledge on malaria, its propagation, prevention and therapy (p. 4-8). As usual, we will look at the current situation of treatment, will name gaps and barriers in supply, for example when the prices of the drugs are too high and the reasons for that (Malaria can be cured, p. 9-11). We will broach the issue of co-infection with HIV in the same way as the particular threat to

children and pregnant women (p. 12), but also the historical connection (p. 13-16). A continuous timeline moreover presents the most important facts in words and pictures. The global WHO combating programs will not be missed out (p. 17-18) and, last but not least, the topic research: read which drugs and vaccines are in the pipeline, which kind of financing models exist and who conducts research on which field (p. 19-25).

“Only few use bednets”, Djékadoum Ndilta from the Republic of Chad/Africa deplores. Our interview with this hospital physician gives an impressive picture of the problems there, but also hopeful approaches (p. 26-27). A safe and effective therapy and good preventive work must go hand in hand – this is the motto.

¹ Julia Meyn: „Mit dem Meer wird man geboren“ Vom Leben an der Küste Nordfrieslands
Reihe: Studien zur Alltagskulturforchung („You are born with the sea“ About life at the coast of North Friesland; Series: Studies on Research of Everyday Culture).
Vol. 5, 2007, p. 23 ff)

2000 B.C.

Malaria: first written mention by the Sumerians



1600 B.C.

First written records in India and Egypt



500 B.C.

HERODOTUS describes the use of mosquito nets in Egypt



1. A little bite with grave consequences

The propagation, transmission and symptoms of malaria

The risk to contract the treacherous malaria after a harmless mosquito bite is distributed very unevenly. In the rich parts of the world, malaria is a threat to only those people who travel to tropical regions. For roughly half of the world's population, however, malaria is the bitter reality of everyday life.

African children under five and pregnant women are particularly affected. The tropical climate creates ideal breeding conditions for the anopheles mosquito which transfers the most dangerous type of malaria, the malaria tropica (plasmodium falciparum). The weak economic systems of the mostly

desperately poor states complicate an effective disease control. Each year morbidity and death cost twelve billion US\$ in severely affected African countries. But roughly five billion US\$ per year would suffice to curb malaria worldwide.¹

Malaria worldwide in 2008

	Cases 2008	Proportion of malaria tropica	Deaths 2008	Proportion of children under 5
Worldwide	243 million	93%	863000	85%
African region	208 million	98%	767000	88%
Southeast Asian region	24 million	56%	52000	77%

Source: WHO, World Malaria Report 2009, Geneva, p. 27

Infection caused by a mosquito bite

Of the 3500 mosquito species, 30-40 can transmit malaria. If an infected mosquito (the female anopheles mosquito) bites a human being, plasmodia will get into the blood circulation. These parasites reproduce in the liver wherein some of them can outlast years and cause relapses (recurrences). If the plasmodia reach the blood, they will infect the red blood cells which burst as a consequence and cause fever. Now the next mosquito that bites the sick person can get the infection during its bloodmeal and transmit the parasite to many other people (see illustration on page 9).² The warmer and more humid the climate is and the larger the number of mosquitoes, the faster this circle will repeat itself.

The symptoms of malaria

About 10-15 days after the bite of an infected mosquito, the patient suffers from headache and vomiting and later also often from fever. Sometimes convulsions and other neurological symptoms culminating in coma occur. Often the symptoms at the beginning of the disease are similar to a simple virus infection. Thus, malaria is often not recognized which is why it is so dangerous. Without treatment or in case of belated treatment, the symptoms can deteriorate and lead to death. For pregnant women, the anemia is particularly dangerous.

400 B.C.

The Greek physician Hippocrates makes a connection between malaria and swamps.



7th century

Written reports about malaria in England



14th century

Malaria epidemic on Korsika



Propagation of malaria worldwide



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities or concerning the delimitation of its frontiers or boundaries. Errors and omissions notwithstanding, the user bears full responsibility for any use of the map.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (PHIGIS)
World Health Organization



Source: WHO 2009

Different types of malaria

The different types of malaria cause different symptoms:

- *Plasmodium falciparum* causes the dangerous and often lethal malaria tropica, which is accompanied by irregular bouts of fever. However, there are no recurrences and the disease can be successfully cured if the patients received treatment in time.
- *Plasmodium vivax* and *Plasmodium ovale* are responsible for malaria tertiana with fever at every third day. Relapses (recurrences) can occur for up to five years, but it can be treated effectively.
- *Plasmodium malariae* gives rise to Malaria quartana. It is characterized by bouts of fever at every fourth day and is the most harmless form of malaria. However, this disease can break out repeatedly over a period of up to 30 years (relapse).³

Malaria tertiana has given the name tertian fever to the disease.

Dangerous epidemics

In those regions where malaria is common, people are repeatedly infected with malaria from a very early age. Those people develop a semi-immunity during the course of their lives. Malaria breaks out to a lesser extent with increasing age and if it does, it is often as a milder form. Children do not yet have such a semi-immunity and are therefore the most frequent fatalities. Large and severe malaria epidemics occur where the anopheles mosquito newly migrates to a region. The population thereof does not have any semi-immunity and within a very short time, many people will be infected. For people with an immunodeficiency, malaria also constitutes a major threat. HIV/AIDS, natural disasters, wars and migrations are likewise factors which favor malaria. They allow morbidity to rise dramatically. (CF)

¹ Global Malaria Action Plan 2008
www.rollbackmalaria.org/gmap/

² Pharma-Brief Special 2/2004, p. 2

³ Gotthard Schettler, Heiner Greten, *Innere Medizin (Internal Medicine)*, vol. 11, 9th Edition 1998, p. 1130-1134

1528

Albrecht Dürer dies of malaria (Infection 1521 in the Netherlands)



17th century

South America: bark of the cinchona tree as an antimalarial drug



1633

Jesuits take the cinchona bark back to Europe. Distribution as „Jesuits' bark“ for the treatment of malaria



2. Malaria can be avoided

With toxins and nets against the mosquito plague

Many states have effectively controlled malaria by consequently implementing the recommendations of the World Health Organization WHO on prevention and therapy. São Tomé and Príncipe, Eritrea, Ruanda and Zambia reduced the fatalities caused by malaria by more than half within the years 2006 and 2008.¹

The WHO recommends two main strategies to prevent malaria: on the one hand, people living in high-risk areas should protect themselves from bites; on the other hand, the propagation of the mosquitoes should be curbed.

Impregnated mosquito nets

Many varieties of the anopheles mosquito bite at night. The best protection against them is a long-lasting insecticide impregnated mosquito net (LLIN). The new nets offer protection for up to three years. Simple insecticide treated mosquito nets (ITN), however, have to be newly impregnated after six months.² The WHO recommends that all persons in high-risk regions should sleep under mosquito nets. Those nets should be provided for the population free of charge. In 2006, only 17% of all African households owned an impregnated net, in 2008 there were at least 31%. But only 22% of African children under the age of five could be protected against malaria with a mosquito net.

WHO's target of reaching a quota of 80% is still miles away. 23 countries of the African region have meanwhile taken up the WHO recommendation and provide impregnated nets for all age groups. 140 million improved mosquito nets were distributed in Africa between the years 2006 and 2008.¹

Spraying indoor walls

The WHO recommends spraying all walls in a room with an insecticide since many mosquito species sit on the wall and rest after their blood meal. The insecticide on the walls kills the mosquitoes. Although it does not directly prevent that the human being is bitten, still it largely prevents the spreading of malaria. However, 80% of the houses in a region have to be sprayed with an insecticide for the measure to be effective (as regards the problems involved with the use of insecticides, see page 8).³ In 2008, 44 countries introduced this preventive measure, among them 19 African countries.

The Costs of Combating Malaria

Mosquito bednets	(Insecticide treated, for 2 persons)	6.40 US\$
Spraying accommodation with insecticides	(Effective for 3-6 months)	7.50 US\$
Malaria test	(Rapid diagnostic test)	0.99 US\$
Therapy with ACT	Adult	1.99 US\$
	Child	0.99 US\$

Average prices in subsidized projects in Asia, Latin America and Africa. Including work and treatment costs. Source: Roll Back Malaria 2009

1658

Oliver Cromwell dies of Malaria



1685

Prince Elector Karl of the Palatine dies of malaria after military exercises at the meadows along the River Rhine near Mannheim



1783

Schiller falls ill with malaria in Mannheim



Destruction of breeding sites

The fact, that a combination of several measures shows the best results, has long been known. From 1929 to 1949, malaria was successfully reduced by environmental measures in the copper mining region of what was then called North-Rhodesia (today Zambia): the breeding sites of the mosquitoes were identified and the plant growth at the riverbanks was removed selectively. Swamps were drained and the courses of rivers were changed. Mosquito nets were mounted at the windows of residential houses.⁴ Current examples from Vietnam, Mexico and Sri Lanka likewise show that an environmental management adapted to the local conditions considerably lowers the number of infections.



Protection for travel

As a rule, travelers from industrial countries have not developed a semi-immunity like the local population (s. p. 5). They are thus particularly in danger of contracting malaria. The Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit (DTG, German Society for Tropical Medicine and International Health) have prepared recommendations for malaria prophylaxis for travelers. Preventative taking of drugs is also included. As a rule, these are drugs which are unsuitable for permanent use in affected countries. Though a part of the drugs approved for malarial therapy can also be used as a preventive – their use without further considerations, however, encourages resistance. If malaria then breaks out, those important drugs are no longer effective – neither as a protection for travelers nor as a therapy for the afflicted. (CF)



Bednets can save lives!

- 1 WHO, World Malaria Report 2009, Geneva www.who.int/malaria/publications/atoz/9789241563901/en/index.html
- 2 Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, U.S.A. www.cdc.gov/malaria/malaria_worldwide/reduction/itn.html
- 3 WHO, Indoor residual spraying, www.who.int/malaria/vector_control/irs/en/index.html and Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, U.S.A. www.cdc.gov/malaria/malaria_worldwide/reduction/irs.html
- 4 Vanessa Laumann. Umweltfreundliche Malariabekämpfung ohne DDT – Strategien und Erfolgsberichte. (Environmentally friendly malaria control without DDT – strategies and success stories) Hamburg 2009: PAN Germany
- 5 Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit (DTG): Empfehlungen zur Malariavorbeugung (German Society for Tropical Medicine and International Health: Recommendations for malaria prophylaxis) www.dtg.org

18th century

The name „malaria“ emerges (attempt at explaining the cause)

Mal-Aria
=
Bad Air

1790

Samuel Hahnemann bases homeopathy on self-experiments with quinine



1817-1876

Regulation of the river Rhine: the drainage of large wetlands contributes to the fight against malaria in Germany



3. Poison the mosquitoes?

DDT in the fight against malaria and its alternatives

The pesticide DDT which has been outlawed worldwide due to its toxicity and persistence is still being used against malaria. There are less toxic alternatives and further sensible methods for controlling the pathogenic *Anopheles* mosquito.



DDT spraying program in Miami/USA in 1948

In 1955, the World Health Organization (WHO) started a campaign for fighting malaria which was mainly based on DDT. Although, mosquito breeding sites and indoor walls were sprayed, only few countries achieved a sustained control of malaria. For this, logistic reasons (the spraying has to be repeated twice a year and has to reach most households) and the development of resistance in the mosquitoes were significant. Moreover, the white deposits on walls and the penetrating odor limited acceptance.¹

In the Sixties, the great number of birds suddenly dying initiated a debate on the toxicity of DDT. The organochloro-insecticide acts in a hormonal manner and is carcinogenic in mammals and, as regards human beings, DDT is suspected to be carcinogenic. At the beginning of the Seventies, DDT was prohibited in many industrial countries. Nevertheless, a further use in combating malaria was considered justified. In 2007, about 4000

tons of DDT were sprayed for controlling the disease.² The Stockholm Convention, which entered into force in 2004, however, aims at ending the use of DDT and other persistent pollutants.³

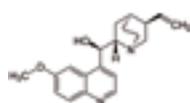
The strategy of the WHO has meanwhile changed significantly. Insecticide treated nets over the bedsteads play the most important role today. For some time, the WHO has also been recommending other pesticides for malaria control, mainly pyrethroids, though they are also relatively toxic to a large extent. A supplementary measure continues to be the spraying of indoor walls. For this, the WHO still recommends i.a. DDT since it has the advantage of a longer effectiveness as compared to other insecticides. However, it is doubtful whether the countries concerned adhere to the strict safety regulations of the Stockholm Convention and (as requested by the WHO) conduct a prior test on the mosquitoes as to DDT resistance.³

What is neglected is the application of non-toxic methods for combating the *Anopheles* mosquito. They could help to drastically reduce the use of insecticides (see page 6). (JS)

- 1 WHO. *Malaria vector control and personal protection*. Geneva 2006
- 2 *Against malaria and leishmaniasis*. UNEP. *Global status of DDT and its alternatives for use in vector control to prevent disease*. Geneva 2008 www.pops.int/documents/ddt/Global_status_of_DDT_SSC_20Oct08.pdf
- 3 Ralph Ahrens and Carina Weber. *DDT and the Stockholm Convention*. Hamburg 2009: Pan Germany www.pan-germany.org/download/ddt/PAN_DDT_Studie_DT.pdf

1820

Isolation of quinine as the active agent of cinchona bark



1826

Malaria epidemic in Norway



1828

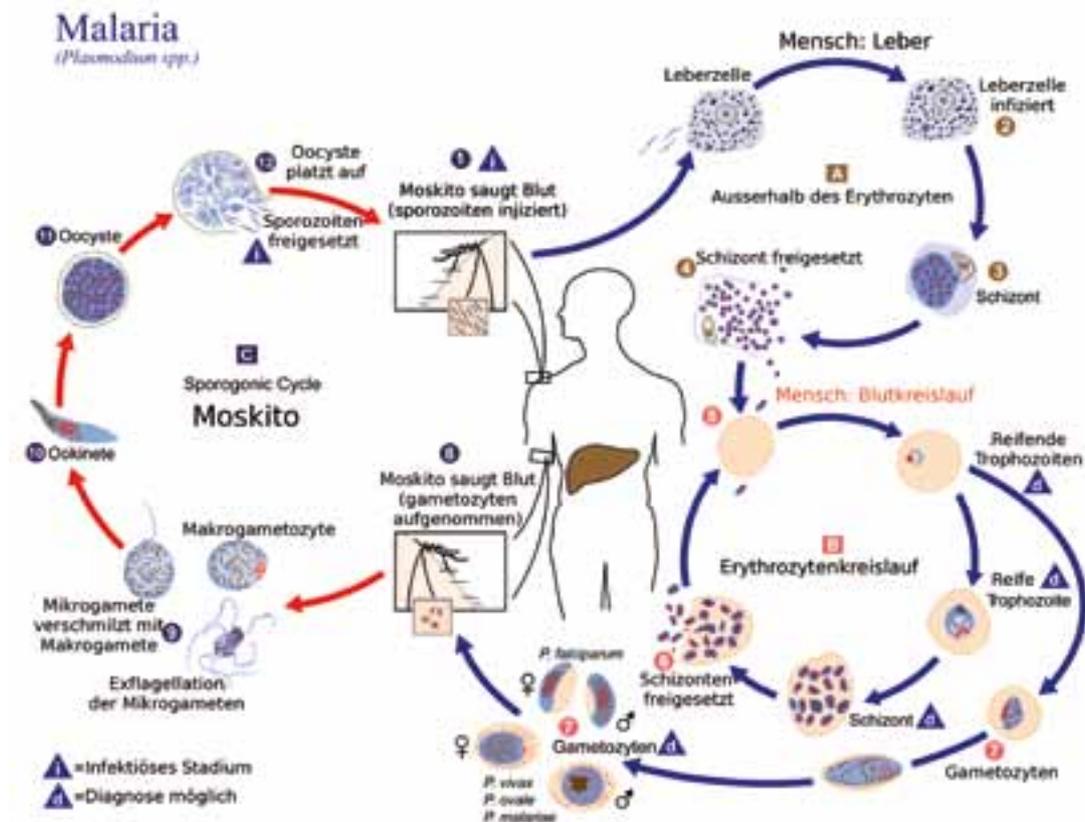
Johann Gottfried Tulla, regulator of the Rhine, dies of malaria



4. To cure malaria means to fight the disease

Diagnosis and therapy of malaria

A timely therapy can effectively fight malaria. It makes sure that the mosquitoes no longer get infected by the sick persons and thus become malarial vectors. The deadly circle is broken.



Life cycle of the malaria pathogen. The plasmodia undergo several stages in the mosquito, in human blood and in the liver of patients. Not every stage is infective. Source: Chb, wikipedia

In countries with relatively few cases of malaria, patients are the foremost source of transmission. A timely therapy therefore not only cures the patient, but it can also prevent numerous new infections and effectively force back malaria in those countries concerned. At the same time the spreading of resistant strains is prevented. In countries with a higher incidence, the sole treatment of the sick is not sufficient to effectively control malaria. Too many people carry the

pathogen in themselves, with which mosquitoes then get infected. Still, therapy cures those affected and prevents many deaths.

At present, several antimalarial drugs are available. Nevertheless, almost one million people die from this disease each year, as more and more pathogens are resistant to the traditional and cost-advantageous drugs. And new preparations are expensive.

1856

First systematic research on malaria prophylaxis by the British Navy



1860s

18,000 workers catch malaria during the construction of the German city Wilhelmshaven



1861-65

During the Civil War in the USA, more than 50% of the troops have a bout of malaria at least once a year.



Hazard caused by resistance

Considerable resistance exists against all malaria drugs, but in particular against chloroquine, amodiaquine and proguanil. What is particularly treacherous is that the patient's symptoms mostly improve for a short while but then they worsen. Death or life-threatening anemia is the result. The WHO has reworded their therapy directive such that the risk of a development of resistance decreases: artemisinin preparations should, e.g. according to the WHO, only be used in combination with other drugs, since a mono-therapy with these preparations encourages the development of resistance. At present, five different combined preparations are available. In many countries, these indispensable drugs are patented which is an important reason for high prices. 85% of malaria-infected African children do not have access to this important medication.

The uncomplicated malaria tropica is treated with the artemisinin-based combination therapy (ACT) for seven days. If that is not effective or if the patients do not tolerate it, reserve preparations are used: artemisinin or even quinine is then combined with tetracycline, doxycycline or clindamycin.

The complicated malaria is a medical emergency: ACTs or quinine are given as an infusion for at least 24 hours. Then the treatment is continued as in the uncomplicated malaria provided the patients can take tablets.

Against malaria tertiana, the still low-priced chloroquine can be used in some countries, if possible in combination with primaquine. In countries with resistance, artemisinin-based combination therapy should also be applied here.

Therapy without diagnosis

The gods placed diagnosis before therapy. This old wisdom is only rarely heeded when dealing with malaria, although the WHO guidelines urgently recommend it. If at all possible, the parasite should be determined before starting the therapy. If a diagnosis is not possible, treatment is carried out based on clinical suspicion. That is the case when patients show the typical symptoms (agues, headache, anemia) of a malarial disease. Concededly, a false diagnosis cannot be ruled out. Some of the patients will therefore receive the wrong treatment and be exposed to grave side effects. Moreover, an unnecessary use of the malarial drugs will favor resistance.¹

It would in any case be safer to prove the parasites in the blood of the patients: the parasites can be shown by a rapid test or under the microscope as a so-called "thick blood smear". Although this rapid test is expensive and not as specific as the diagnosis with a microscope, it can also be used in situations in which no microscope is available. Of those African patients treated for malaria, the parasites were shown in only 22% of the cases in 2008. The large majority was treated purely on clinical suspicion.² So the field of malarial diagnosis still leaves much to do! Access to low-priced and effective malarial rapid tests is an essential prerequisite for an effective and safe anti-malarial treatment in poor countries. (CF)

1865

Malaria epidemic in Paris



1880

Algeria: discovery of plasmodia as the malarial pathogen (Alphonse Laveran)



1883

Demonstration of the malarial pathogen's life cycle in the mosquito (Ronald Ross)



Overview of antimalarial medicines and their most important undesirable effects.³

All antimalarial medicines can cause more or less severe side effects, some can even severely damage the health of the patient. Above all, gastrointestinal problems occur.

Drug	Use, Resistance	Resistance	Particularities ⁴
Amodiaquine	Therapy chloroquine-resistant strains	frequent	Tolerated worse than chloroquine. Damage to liver and heart
Antibiotics: Tetracycline, Doxycycline, Clindamycin	Therapy		i.a. impaired growth in children (tetracycline and doxycycline)
Artemisinin and its derivatives (e.g. artemotil, artesunate)	Prophylaxis and therapy. Use only in combination in order to prevent resistance	rare	Side effects rare
Atovaquone/ Proguanile	Prevention and therapy, resistance against the single substance thus only in combination therapy	frequent	
Chloroquine	Prevention and therapy against malaria tertiana and quartana in regions without resistance	very frequent	Mostly well tolerated. Side effects i.a. impaired vision
Mefloquine	Prophylaxis and therapy		Side effects frequently psychoses i.a.
Primaquine	Therapy: reduces the infectiveness of the pathogen in the blood, thereby reducing the spreading of malaria		Side effect: digestive disorders, anemia i.a.
Pyrimethamine	Prophylaxis: in combination with sulfonamides Therapy: in combination with dapsone		
Sulfadoxine/ Pyrimethamine	Only therapy		Frequent side effects: digestive disorders, psychoses i.e.

1 WHO, *Guidelines for the Treatment of Malaria 2nd ed. 2009*, Geneva, p. 9-12 http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (29.4.1010)

2 WHO, *World Malaria Report 2009*, Geneva, p. IX-X www.who.int/malaria/publications/atoz/9789241563901/en/index.html (14.4.2010)

3 WHO, *Guidelines for the Treatment of Malaria 2nd ed. 2009*, Geneva, p. 73-109 http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (2.6.1010)

4 The table only contains some examples of the most important side effects; details can be found under: WHO, *Guidelines for the Treatment of Malaria 2nd ed. 2009*, Geneva, p. 73-109 http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf

1885

The Italian CAMILLO GOLGI (1844-1926) identifies the malaria pathogen *Plasmodium vivax* and *Plasmodium malariae*.



1897

The *Anopheles* mosquito is identified as the transmitter of malaria



1898

The first tropical institute of the world opens in Liverpool



5. Poverty renders malaria a deadly danger

Children and pregnant women are particularly affected

Every 30 seconds, a child dies of malaria. Their immune systems have not yet developed a protection against the disease. Likewise, malaria is a deadly danger for AIDS-patients because of the HIV-related immune-deficiency.

In Southern Africa, 16% of infant fatalities are caused by malaria. 88% of the fatalities caused by malaria in 2008, were children under 5. Children suffering from malaria could survive if they had access to the new artemisinin-based combination treatment (ACT) with few side effects. However, these important drugs are often unachievable and too expensive for poor people. Though many governments have officially agreed to the WHO – recommended change to newer more tolerable drugs, the reality looks somewhat different: in 2008 only 15% of the children with malaria received this treatment in Africa.

The by-far larger part of the little patients had to make do with household remedies or with the low-priced chloroquine which has meanwhile become largely ineffective.¹

Risk: poverty and malnutrition

Those families often even lack the money for the bus trip to the next health care center. Many parents therefore treat their sick child with household remedies (see Interview on page 26). In the health care centers, a malaria test is often not carried out since access to simple diagnostics is scarce. Children with fever are simply treated against malaria. The unnecessary use of the longstanding drugs encourages resistance and further deteriorates the situation.

Likewise, pregnant women are particularly affected: in 2008, 50 million pregnant women had malaria. The anemia caused by malaria endangers the mother-to-be and the unborn child. Only 20% of the pregnant women in Africa had access to necessary medication.² Malnutrition and malaria often go side by side and increase the risks. In case of malnourished patients, the medication is not as effective as in the case of well-nourished contemporaries

Malaria and HIV

HIV and malaria are a fatal combination in Southern Africa. The course of the disease is dramatic in AIDS-patients, complications and death are frequent. The malaria drugs are not that effective in their cases and some preparations cannot be used due to interactions with AIDS drugs.³ (CF)

- 1 WHO, *World Malaria Report 2009*, Geneva, p. IX www.who.int/malaria/publications/atoz/9789241563901/en/index.html (14.4.2010)
- 2 UNICEF, *Malaria & Children, Progress in Intervention Coverage*. Geneva 2009. www.unicef.de/fileadmin/content_media/presse/0904-Malaria/malaria_and_children_2009.pdf
- 3 WHO, *Guidelines for the Treatment of Malaria 2nd ed.*, Geneva 2009, p. 32-33 http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf

1900

Foundation of the „Institut für Schiff- und Tropenkrankheiten“ (“Institute for ship-and tropical diseases” at the Hamburg harbor (today the Bernhard-Nocht-Institute)



1906-16

Systematic fight against mosquitoes makes the construction of the Panama Canal possible (malaria in workers is reduced from 82% to 7%)





Before it was straightened, the River Rhine offered a diverse habitat for mosquitoes as malarial vectors. (Picture: Isteiner Klotz, Peter Birmann 1810)

6. When tertian fever was still terrifying

Malaria in Germany

Over centuries, malaria was a dreaded disease in many parts of Germany. The German poet Friedrich Schiller caught malaria. Tulla, the person who straightened the River Rhine, was killed by tertian fever.

Tertian or marsh fever, that is what the generation of our great-grandparents called malaria – a disease which caused fear and terror in Europe. The Italian term malaria means “bad air” and stems from a time when the cause of malaria was still unknown. In Italy, the Po valley was a well-known malaria region. But even in the Netherlands, in Russia and in Sweden did this disease occur. In Austria, tablets against malaria were distributed among school children as late as 1945.

In Germany, malaria affected above all North-German moorlands and the South-German region of the Upper Rhine. Before being straightened, the River Rhine had a

width of up to four kilometers and looped through the landscape. In spring, when the snow melted, the river often swelled to a width of 12 kilometers. As a consequence of torrential floods, the Rhine continually changed its course. Riverside woodlands and swamps characterized the landscape. Together with the warm climate, these were ideal conditions for the malarial vector – the anopheles mosquito.¹

The fight against mosquitoes

The situation at the Upper Rhine was difficult. Villages again and again fell victim to the floods. The permanent

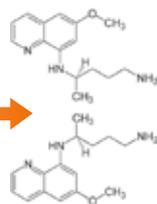
1914

Foundation of the tropical clinic in Tübingen



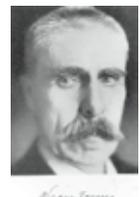
1926

Synthesis of primaquine: the first synthetic antimalarial drug



1927

The Nobel prize for medicine goes to Julius Wagner-Jauregg for an artificial malarial infection for the treatment of syphilis



redirection of the riverbed often resulted in boundary disputes between France and the German small states. A straightening of the Rhine should eliminate both problems. As a result of entanglements of foreign policy, however, this project took more than 100 years.² The drainage of the Rhine floodplains was a massive ecological interference. It eliminated malaria, but also forced out numerous animal species and many fishermen lost their livelihood.

The situation in Northern Germany was similar. Many wetlands, marshes and regularly flooded areas offered perfect breeding conditions to mosquitoes. At the construction of the city of Wilhelmshaven in the 1860ies, 18,000 workers fell ill with malaria.³

Since the 16th century, cinchona bark was available as a remedy and, since 1820, the quinine isolated from the bark, which still has its place in malarial therapy even today. When the method of transfer was determined, many further activities, in addition to draining the swamps, were initiated to eradicate malaria. For example, the mosquitoes' larvae were killed by pouring kerosene into stagnant waters. The mosquitoes themselves were controlled with insecticides. From the years 1920 to 1950, most of the currently used malaria drugs were developed.

Germany is freed of malaria

Towards the end of the 19th century, malaria retreated from Europe.⁴ From the outset, the vector found worse conditions for development in these temperate climate zones here than in tropical or sub-tropical areas.⁵ The drainage of the swamps and the destruction of the mosquito breeding sites achieved the rest. In Germany, the cases of malaria were limited to the estuaries of the large

rivers and effective medication had been found, which could be dosed exactly and with which the disease could be treated well. This did not only cure the patients but the mosquitoes acquired the malarial pathogen to a much lesser degree.

This was undermined by improved hygiene: stables and the fact that the animals were kept in the dwellings offered good living conditions for the mosquitoes. In warm, dark and humid rooms, parasites could develop even if the temperatures outside were lower. When human beings and animals stopped living together at such close quarters, when the dwellings became lighter and drier and open sewage and mud floors disappeared, the habitat of the mosquito was reduced. The population shrank and the number of malaria cases decreased.

Under the conditions of and after World War II, the living conditions in Germany deteriorated again. In the region of the Upper Rhine, there was a last flaring of domestic malaria with about 30 cases during 1945 and 1947. Soldiers returning home also brought along malaria. During the first years after the war, about 2000 people were infected in Germany per year. However, the number of infections quickly decreased again and since 1951, malaria is seen as eradicated in Germany.⁶ (CF)

- 1 www.am-kaiserstuhl.de/Natur/rhein.htm (2,5.2010)
- 2 Christoph Bernhard, *Die Rheinkorrektion, in Der Rhein (The correction of the River Rhine, in The River Rhine,)* booklet 2000/02, p. 76-82, www.lpb.bwue.de/aktuell/bis/2_00/rhein03.htm (3,5.2010)
- 3 David Blackburn, *Die Eroberung der Natur. Eine Geschichte der deutschen Landschaft. München 2007 (The Conquest of Nature. Water, Landscape and the Making of Modern Germany. London 2006)*
- 4 Erwin Ackerknecht, *Geschichte und Geographie der wichtigsten Krankheiten (History and geography of the most important diseases)*. Stuttgart 1963
- 5 H. Horstmann, *Malaria in Deutschland (Malaria in Germany) 1945-1947, Zeitschrift für Tropenmedizin und Parasitologie (Magazine for tropical medicine and parasitology)* 1 (1), 1949, p. 57.
- 6 Irfan Sarwar, *Malaria am Oberrhein, Inauguraldissertation (Malaria at the Upper Rhine, inaugural dissertation)*, Heidelberg 2002, p. 105-127, 150-155

1928

Italy: drainage of swamps exterminates malaria



1933

Screening of 14,000 substance by US army research (Walter Reed Institute) during the search of an antimalarial drug



1934

Synthesis of chloroquine (Resochin®) by Bayer

7. Colonial Power and Military Research

The history of antimalarial drugs

The history of the fight against malaria is closely connected with colonial rule and military interests. Research was not at all aimed at helping those populations who were most severely plagued by malaria but at helping Europeans and Americans.



Since the 1980s US army is working on a malaria vaccine

„Tropical research is an instrument of imperialistic politics“, explained the British Secretary of State J. Chamberlain when he opened the first tropical institute of the world in Liverpool in 1898.¹ He got to the heart of the problem: tropical diseases threatened colonial rule. 85% of all Europeans who travelled to West Africa died of malaria or sustained permanent damages. In colonial regions, more military personnel were killed by malaria than by weapons.²

Dutch quinine monopoly

Quinine, the first antimalarial drug known in Europe, originates from Peru. In the cold mines of the then Spanish

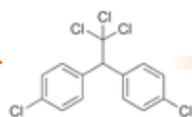
colony, the workers often suffered from the agues. Jesuit Physicians observed in the 16th century that the Peruvians used the bark of the cinchona tree to lower the fever. The message that a remedy against malaria had been found spread quickly.³ The “bark of the china tree”, as it was later incorrectly named in Germany, started its triumphal success in 1630. At that time, malaria was still widely spread in Europe and the need for the “Jesuit powder” or “Peruvian bark” was such that even other colonial powers tried to enter this business. Large plantations of cinchona ledgeriana were responsible for the circumstance that Holland enjoyed almost a monopoly position at the end of the 19th century. As late as 1939, 80% of the world’s production of quinine originated in the Dutch colonies.⁴ But the British had also started cinchona plantations in their colonies.⁵

Tropical medicine and German patriotism

In the 20th century, the research of new drugs started. As a first synthetic active agent, plasmoquine was developed in 1926, which is the predecessor of primaquine. In 1932, mepacrine (Atabrine®) followed; in 1934 the pharmaceutical Bayer-Werke invented chloroquine (Resochine®).⁶ At that time, Germany had long lost its colonies. It was suggested to those German researchers by their international colleagues to relinquish their ambitions

1939

Synthesis of the insecticide DDT (Paul Müller)



1940

Malaria is eradicated in the USA.



1944

Artificial production of Quinine



towards tropical medicine, to which patriotic German scientists countered: their research fervor should prove that Germans had a right to those colonies.⁷ There were strong reservations about chloroquine as a result of its alleged toxicity,^{8,9} which is why Bayer developed sontoquine® (3-methyl-chloroquine) as a variation.¹⁰ Even during the Second World War, heated debates were held about the publication of this secret Bayer invention. It should be prevented that the USA could forestall the Germans with a new antimalarial drug.

Malaria and the US army

In order to improve medical care for soldiers, the USA founded the Walter Reed Institute¹¹ as early as 1893 as an army-owned research institution. Malaria was a problem even in the USA: during the American Civil War from 1861 to 1865, more than half of the soldiers suffered from malaria attacks, which were treated with more than 25,000 kg of quinine. Even before entering into the Second World War, it was clear that an independent supply with antimalarial drugs had to be set up. The USA were still dependent on the quinine supply from the Dutch colonies and those were highly endangered by their geographic closeness to Japan.

After a screening of 14,000 substances at the Walter Reed Institute, mepacrine hydrochloride (atabrine®) was developed and later mepacrine mesylate (quinacrine®). After the end of the World War II, the repertoire was enlarged with two products of British industrial research (1945 proguanil and 1952 pyrimethamine of Wellcome). However, the most effective and important drug proved to be the German chloroquine.

When in the course of the worldwide fight against malaria, more and more

parasite resistance against chloroquine emerged, the US military research became active again. The trigger was the Vietnam War: the massive number of US soldiers who died from malaria made new drugs necessary. The research of more than 250,000 substances at the Walter Reed Institute resulted in the development of mefloquine and halofantrine.¹²

Old Chinese plants in a new light

With a few exceptions, the interest of civil research in malaria was slight. In the eighties, the US military started with research on a vaccine. The great “civil” breakthrough was achieved by Chinese scientists in the eighties with their research on artemisia annua, the annual mugwort. From this Chinese medicinal plant with its tradition of over 2000 years, a whole series of new active agents were derived. And finally, the needs of the civil population have been placed at the center of focus of scientific interests. (CW)

- 1 Hansjakob Baumgartner, *Malaria: Resistenz rentiert* (Resistance is worth it). Südwind 8/1983 p. 11
- 2 Manson's *Tropical Diseases*, 21st Edition 2003
- 3 Quinine was isolated as an active agent in 1820 and has been in use in therapy as a pure substance ever since.
- 4 Irwin W. Sherman (editor.); *Malaria: Parasite Biology, Pathogenesis, and Protection*, ASM Press, Washington 1998. Cited according to Giger, *Rückblick in die Geschichte der Malaria und historische Behandlungsmethoden* (A retrospective look at the history of malaria and historical treatment methods) www.gigers.com/matthias/malaria/history.htm
- 5 Rohan Deb Roy *Malarial connections: British India and beyond, 1820-1912*. WellcomeHistory Issue 2010, 43, 10-11
- 6 *The antimalarial drugs, history*. In: Manson's *Tropical Diseases* 25th edition, Edinburgh 2003
- 7 F. Hansen, *Vom Kolonialismus zur Geomedizin. Geschichte der Deutschen Gesellschaft für Tropenmedizin und Internationale Gesundheit* (From colonialism to geo-medicine. The history of the German Society for Tropical Medicine and International Health) www.dtg.org/uploads/media/Geschichte_der_DTG.pdf; Sven Tode, *Forschen-Heilen-Lehren: 100 Jahre Hamburger Tropeninstitut* (Research-Healing-Teaching: 100 years of the Hamburg Tropical Institute). In: Bernhard-Nocht-Institut für Tropenmedizin 1900-2000, Hamburg 2000.
- 8 Chloroquine was only used after 1946.
- 9 J. Wiesner et al., *Neue Antimalaria-Wirkstoffe* (New antimalarial active agents). *Angew. Chem.* 2003, 115, 5432-5451
- 10 Today, chloroquine phosphate is mostly used.
- 11 Walter Reed Army Institute of Research www.wrair.army.mil
- 12 *Geo Wissen Abwehr, Aids, Allergie* (Magazine Geo Knowledge Defense, Aids, Allergies). No. 1/1988

1947

Last flare-up of domestic malaria in Germany (30 cases at the Upper Rhine)



1948

The liver stage of Plasmodium vivax is identified



1950

First antimalarial control with DDT





Treatment in time or even a malaria vaccine could save millions of childrens lives.

8. The worldwide fight against malaria

Strategies and concepts of the WHO

Since the 1950ies, the World Health Organization (WHO) has tried to coordinate the fight against malaria worldwide. The concepts have changed in the course of time but the problems still continue to be the same.

The WHO started their first program for the eradication of malaria in 1956. The most important tool was the insecticide DDT and the drug chloroquine, which was used for prophylaxis and as therapy. At first, the efforts seemed to be crowned with success. In several countries, malaria was on the verge of eradication: in Sri Lanka, only 20 cases were counted in 1963. But in the Seventies, the tables turned: DDT had lost its effectiveness as a result of its large-scale application (also in agriculture). At the same time, the malarial pathogen became increasingly resistant against chloroquine. Irrigation projects created new habitats for the

mosquitoes. And last but not least, political and armed conflicts were responsible for the discontinuation of many malaria programs in Africa and Asia. The pharmaceutical industry on their part had lost interest in the development of new drugs since malaria, as a disease of the poor, was unprofitable.

A new attempt

In 1998, a new attempt was initiated: the Roll Back Malaria Program (RBM).¹ At that time, the concept of “partnerships” had become popular. A network was created which should coordinate the manifold

1951

Malaria is pronounced eradicated in Germany



1957

First reports on chloroquine resistant Plasmodium falciparum pathogens in Southeast Asia



activities, e.g. to ensure medical supply, to train the medical personnel in the correct use of the medication, to distribute bednets and to scientifically accompany the use of insecticides. The program was adapted to the respective regional context.

For many years, RBM had been a loose union. The new structure of 2006 rendered it more binding. Today altogether seven pillars support the alliance: academic research, the governments of the countries concerned, money-donating foundations (Gates et al.), multilateral organizations (WHO, UNICEF, UNDP, World bank), NGOs, OECD-donor countries (e.g. Italy, Great Britain, the USA) as well as the private sector (pharmaceutical companies). This list clearly shows that it is very broad alliance and that the WHO is only one of many actors, some with strong self-interests. In 2008 the activities were organized in a Global Malaria Action Plan.²

New actors

The financing of malaria control necessitates considerable financial funds. For that reason, the then UN General Secretary Kofi Annan demanded the installation of a Global Fund in 2001, which is to provide and channel additional funds. In 2002, the time had come: the Global Fund for fighting AIDS, tuberculosis and malaria was founded, in which the WHO did not have voting rights, but the industry did. Nevertheless, the Fund has meanwhile become a quite effective financial instrument. It does not have its own malaria control concept but exclusively supports regionally developed measures. Any country which applies with its projects has to present a well worked-out concept for therapy and prevention, the implementation of which should be continually supervised

Enormous financial gap

For combating malaria, 104 million insecticide-treated bednets have been distributed, 19 million insecticide treatments of dwellings have been financed and 108 million malaria therapies have been paid. 5.3 billion US\$ were invested into the malaria programs of 83 countries.³ In comparison to HIV/AIDS, malaria leads a shadowy existence within the Global Fund. However, the Fund has sharpened the public awareness for malaria.

At the moment, the Global Fund is faced with a large financial gap. According to the calculations of the Global Malaria Action Plan, an annual amount of 5.9 billion US\$ would be necessary.⁴ If there are no additional funds, applications for programs that could be well realized would have to be rejected. In October 2010, a “replenishment conference” will therefore take place in New York.

One name has meanwhile been connected to almost all measures: Bill Gates. The founder of Microsoft invests several hundred million US\$ in health programs and research via the Bill&Melinda Gates Foundation. Gates has thus become the most important sponsor. This does create new possibilities for action; however, it also creates a large dependency. (CW)

1 www.rbm.who.int/
 2 www.rollbackmalaria.org/gmap/
 3 *The Global Fund 2010: Innovation and Impact. March 2010*
 4 *Resource Scenarios 2011-2013. Funding the Global Fight against HIV/AIDS, Tuberculosis and Malaria (2010)*

1958

The WHO initiates strategies for the worldwide eradication of malaria.



1959

Chloroquine resistant pathogens in the Amazonas region



1967

WHO declares the malaria extermination to have failed

9. Many coffers and many actors

Insights into malaria research

Hardly any other field of research has changed so much in recent years as the research on malaria. Today it is characterized by worldwide networks with a strong African participation. Product Development Partnerships combine industrial and non-commercial actors. Clinical studies are often planned and carried out by non-commercial institutions. Its financing has also changed.

The research on malaria is directed at two targets: new antimalarial drugs and vaccines. The former are desperately needed since the treatment with artemisinin combined preparations can become ineffective by the development of resistance in the foreseeable future. The latter could disrupt the vicious cycle of infection and propagation (page 23).

New antimalarial drugs

Four Product Development Partnerships are engaged in the development of new therapies. The largest is the Malaria Medicines Venture (MMV). It cooperates with about 80 research institutions and several companies, and so far, the organization has put an artemisinin combined therapy for children (Coartem® Dispersible by Novartis) on the market. Coarsucam of sanofi-aventis and Eurartesim® by Sigma-Tau are on the verge of approval. A project with German participation is likewise far advanced: IV artesunate is in phase II of the clinical studies at the University of Tübingen. 19 new groups of active agents are in the pipeline of MMV; the current projects equally originate from industry and public laboratories.¹

The financial plan provides a budget of 470 million US\$ for the years 2000 to 2015. The most important investors are the Gates Foundation (63%), Great Britain (12%) and the Netherlands

(4%). The funds are mainly invested in research, 6% go into care programs with patented MMV products. Generic products are not planned – probably because of the prominent status of the large pharmaceutical companies within the MMV.

Low-priced raw materials

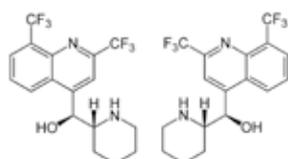
Two further Product Development Partnerships are dedicated to the artemisinin research. The Gates Foundation finances this project as the „Artemisinin Enterprise“. One of them involves the Institute for One World Health (iOWH)². It is engaged in product development on the basis of genetically engineered artemisinin. The technology originates from the University of California Berkeley, which signed, in accordance with the model „Equitable Licensing“³, two varying license agreements: one with the iOWH (non-profit) and one with Amyris Biotechnologies (for profit). Since 2008 the iOWH has cooperated with sanofi-aventis in order to realize production in large quantities.

The University of York and Médiplant (Switzerland) count on plant production: high-performance artemisia varieties are bred with biotechnological breeding methods but without genetic engineering.

The Drugs for Neglected Disease Initiative

1971

Mefloquine is used for the treatment of malaria for the first time.



1972

China: Artemisinin is isolated from the annual mugwort



(DNDi)⁴, a group of several research institutes in Africa, Asia and Latin America, has developed two combined preparations which have reached approval stage: artesunate + mefloquine and artesunate + amodiaquine. What is special about this concept is the fact that both products have been developed without patent protection and can be produced as generics in the future. The production of a vaccine is attended to by the Malaria Vaccine Initiative (MVI, see p. 23). In contrast, the work of the IVCC, in which mostly tropical institutes and manufacturers of pesticides cooperate, is directed at the control of mosquitoes.⁵ The target is the optimization of insecticide-impregnated bednets and other pesticide-based methods. The improvement of the malaria diagnosis is the target of FIND.

Financing

In 2008 542 million US\$ were invested in the malaria research worldwide.⁶ Most of the money originates from the public purse or from private donators (together 83%): number one is the Gates Foundation (174 million = 32%), followed by the US National Institutes of Health (19%) and the pharmaceutical industry (17%). The US Ministry of Defense ranks 4, Germany is at the far back. The funds were spent for pharmaceutical research (32%), development of a vaccine (32%), basic research (25%), mosquito control (vector control, 2%) and diagnostics (1%).

Malaria is gradually leaving the field of “neglected diseases” and the activities of the companies are expanding. GlaxoSmithKline set up an “open laboratory” in Spain, in which 60 researchers carry out their own projects each year utilizing the infrastructure of GSK. The latest venture is the

announcement that 13,500 active agents which are suitable as antimalarial drugs shall be published from the company’s own collection of active agents. They shall be made available as “public domain” with all relevant data.⁷

Drug approval

Together with the growing interest in research, the framework conditions have also changed – above all in Africa. More and more clinical studies take place there, for which the legal conditions and control mechanisms have to be created. Moreover, new drugs are being developed which are tailored to the needs of African countries. They have to be registered without the customary preliminary work from European or US-American approval authorities. All this necessitates high-performance national authorities which cooperate transnationally and regionally.⁸ (CW)

- 1 *MMV at a Glance: 10 years of successful malaria drug research.* (2009)
- 2 *Institute for OneWorld Health, Malaria Fact Sheet* www.oneworldhealth.org/img/pdfdownloads/Malaria%20Fact%20Sheet.pdf (4.6.2010)
- 3 *see Pharma-Brief Special 1/2009*
- 4 www.dndi.org
- 5 www.ivcc.com
- 6 *Mary Moran et al. G-Finder: Neglected Disease Research & Development: New Times, New Trends.* Sydney 2009.
- 7 *Andrew Witty: Remarks Delivered at the Council on Foreign Relations, New York 20.1.2010.*
- 8 *DNDi, George Insitute: Registering new drugs. The African context.* Sydney 2010. www.dndi.org/regulatory.html

1975

Foundation of the Special Program for Research and Training in Tropical Diseases (TDR) by the WHO, UNICEF, UNDEP and the World bank



1980s

Chloroquine resistant *Plasmodium falciparum* pathogens spread in tropical Africa.



10. Affordable medication

Subsidies and more competition

The production of the combination preparations (ACT) recommended by the WHO is significantly more expensive than the “classic” chloroquine. In order to make the drugs affordable, there are several strategies. Although a pricing pressure through competitors (generic drugs) is important, even then the drugs are too expensive for the poor. In this situation only subsidies will help.

All recommended antimalarial medication is based on artemisinin. This active agent is produced from plants and, according to the drug, is chemically changed. No matter who produces the drugs: the production is too expensive: ACTs cost up to ten times the amount of the traditionally used medication. Whereas the price for the treatment with chloroquine is about 7 Euro-Cent, the treatment with artemether/lumefantrine costs around one Euro, the one with artesunate/amodiaquine about Euro 1.70.

Lowering the production costs

The plant *Artemisia annua* is cultivated in many regions of the world. Its price had been subject to strong fluctuations for years. Top prices of 1200 US\$ per kilogram active agent promised good business. However, when the market price of 200 US\$ dropped below the production costs, many farmers were induced to withdraw from this field and a supply shortfall threatened.¹ MMV organizes annual congresses on *Artemisia* production,² in order to guarantee price reliability for farmers and supply reliability for manufacturers. UNITAID established a specific credit program to support the cultivation and processing of *artemisia* independent of market fluctuations.³ Thus, the prices for the raw material artemisinin could be stabilized at about 300 US\$ per kilogram. It has also been attempted to produce artemisinin

artificially or to increase the content of active agent in the plant by breeding (see p. 19). However, the costs are still too high for the patients.

Competition lowers the price

It is also competition that lowers the price. For all combination preparations, there are several manufacturers – at least for those products which offer the two active agents in separate tablets (co-blisters). Most manufacturers are located in India and China. If the active agents are combined in one tablet (fixed-dose combinations), there is less

Price per treatment:¹

Chloroquin	0,07 €
Artemether/Lumefantrine	1,08 €
Artesunate/Amodiaquine	1,74 €

competition. The market leaders in this field are Novartis (coartem = artemether + lumefantrine) and sanofi-aventis (coarsucam = artesunate + amodiaquine). Two manufacturers of generic products from India have already passed the quality test of the WHO. Coarsucam has so far only been produced by sanofi-aventis in Marocco. That is astonishing since the drug is not covered by a patent and was developed jointly with the Drugs for Neglected Disease Initiative DNDi. It is sold at the cost of manufacture of one US\$ per therapy. It seems that the low price renders coarsucam unattractive.

1998

Foundation of WHO Roll Back Malaria Program



1999

Foundation of Medicines for Malaria Venture



Meanwhile two Indian producers have obtained a WHO pre-qualification for the production.⁴ So the chances are good that coarsucam generics will also be put on the market soon. The “1-dollar-therapy” with coarsucam has developed to be a kind of benchmark price, which resulted in significant price reductions for the rival product coartem. The only further new development not covered by a patent – the drug lapdap – was taken from the market because of health risks in 2008.⁵

Affordable Medicines Facility – Malaria (AMFm)

The last option for lowering the price is to subsidize the selling price. In 2008 a new financial instrument was created for this purpose: the Affordable Medicines Facility (AMFm). It is affiliated to the Global Fund and is aimed at pushing the price down to 5 US-Cent per treatment.⁶ AMFm buys the antimalarial drugs at a price of 0.24 to 1.43 US\$ per treatment and offers them for an estimated 5 US-Cent. The difference in price will be taken over by UNITAID, the British Government and the Gates Foundation; the overall costs are estimated to be 216 million US\$. The final price which the patients have to pay out of their own pockets will presumably lie between 20 and 50 US-Cent. AMFm is currently being tested in ten countries.

Establishing ATCs on the private market

Purchasers of the low-priced antimalarial drugs could be public institutions (e.g. ministries of health), non-governmental organizations and privates (e.g. wholesalers). AMFm is not only intended to reach the classic health programs but also to increase the proportion of ACTs in the private sector. About 60% of the patients buy their antimalarial

medication on the private market. However, the proportion of ACTs only amounts to 5%. Pilot studies in Uganda and Tanzania showed that, by reducing the price, more ACTs were quickly found on the market.⁷ This is also the reason for criticizing AMFm,⁸ since the improper use of privately purchased ACT supports the formation of resistance if, for example, a patient does not have enough money to buy tablets for the complete therapy. Another point criticized is the sale of co-blisters packages (which contain different tablets with one active agent each). In this way, patients can resell single tablets – that means monotherapies. Thus the path for more resistant malaria pathogens would be prepared.

AMFm wants to prevent this incorrect use of the drugs by a comprehensive accompanying program. This educational and advisory work will cost about 127 million US\$ in the pilot phase. That amount has to be provided by the Global Fund. (CW)

- 1 www.mmv.org/sites/default/files/uploads/docs/artemisinin/2008_event/12_Will_Wang_-_Guilin_Pharma_20081125.pdf
- 2 Artemisinin Forum 2008-2009
- 3 Assured Artemisinin Supply System AzS2 www.azs2.org/
- 4 WHO World Malaria Report. Geneva 2009.
- 5 Update on GSK's malaria treatments: Dacart and Lapdap. 29.2.2008. www.gsk.com/media/pressreleases/2008/2008_pressrelease_0014.htm (4.6.2010)
- 6 All following calculations are from: AMFm Frequently Asked Questions, of 29th March 2010
- 7 *Lancet* 2009, 374, 1224-1226
- 8 *Lancet* 2010, 375, 121

2002

Foundation of the Global Fund to Fight AIDS, Tuberculosis and Malaria



2002

Genome of *Anopheles gambiae* decoded



11. Vaccinal protection against malaria?

Worldwide projects are directed at the development of a vaccine

A vaccination against malaria could spare much suffering. But as yet it does not exist. For decades, a vaccination against malaria has been a scientific challenge: it would be the first vaccination against parasite. One candidate for a vaccine has reached such a stage in its development that it may be put on the market within a few years.

The vaccine with the name RTS,S is being co-developed by GlaxoSmithKline and the Malaria Vaccine Initiative (MVI).¹ At present, the last clinical studies are run in Africa. Although RTS,S has so far only shown limited effectiveness, it would be a first step. At the most the vaccination reduces the risk of malaria by half and the protection would only be for a limited period of time. RTS,S was originally developed by the US-military in the Eighties and sold to GSK.² The costs for the clinical studies are shared by the pharmaceutical company and the MVI. The MVI contributes 200 million US\$, which originate from the Gates Foundation. In return, GSK assured that the vaccine, which is exclusively intended for Africa, will be offered at an advantageous price. A vague statement, a definite guarantee for a patent-free product is missing. However, without the MVI financing, there would hardly have been any clinical studies. Before the MVI entered the stage, GSK was on the point of ceasing the work on RTS,S. Yet, the project should be profitable for the company: the vaccination contains a new enhancer (adjuvants) which is sure to enter other research work as well.

When the MVI began its work, RTS,S was the only candidate promising success within the foreseeable future. Meanwhile, work is carried out on many competing vaccinal concepts, which

focus on different stages of the life cycle of the parasites. Most concepts are still at the primary stage and their future is uncertain. Since the malarial pathogen varies strongly genetically, the challenge is impressive.

Purchase guarantees for the manufacturer

A financing concept is interesting which was created for the development of a malaria vaccination. Advanced Market Commitments offer a producer a guaranteed purchase for a newly developed vaccine. This should create a calculable market so that companies undertake investments. This concept should actually boost malaria research, but presently it finances a pneumococcal vaccine. Since corresponding vaccines are already on the market, the basic idea – the creation of an incentive for research – was reduced to absurdity. Advanced Market Commitments in their present form have become an industrial subsidy. Those funds could be used more effectively for other vaccine projects – for example against malaria.³ (CW)

- 1 www.malariavaccine.org
- 2 Paul Wilson: *Giving developing countries the best shot: An overview of vaccine access and R&D.* OXFAM, MSF (2010)
- 3 Donald W. Light (2009), *Advanced Market Commitments Current Realities and Alternate Approaches* www.haiweb.org/31032009/27%20Mar%202009%20AMC%20Current%20Realities%20&%20Alternate%20Approaches%20FINAL.pdf

2003

Patent free Lapdap®
(Chloroquine + Dapsone)
is registered



2004

ART/LUM fixed-dose
combination Coartem®
approved for children



2006

BNI Hamburg: Merosomes
discovered as pathogenic
stage

12. Germany's Research Landscape

Who is researching what, where and with whom?

German research institutions are also taking a part in the research and fight against malaria. All institutions are integrated in international networks and often cooperate with African and Asian partners.



The Bernhard-Nocht-Institute in Hamburg, founded as the "Institute for Ship and Tropical Diseases" in 1900.

In addition to large projects, which are mostly handled by tropical institutes, there are smaller projects at other universities, e.g. in Bonn, Düsseldorf and Gießen. They research the chemical synthesis of new active agents or active agents in medicinal plants.

The research can be divided into two categories. The basic research is directed at the malarial pathogen and at the processes in the body of the mosquito and in the human being in order to find new approaches for prevention and therapy. Clinical research is addressed at those already infected or those who should be protected from an infection.

Berlin: Charité

The Institute for Tropical Medicine at the Berlin Charité¹ is engaged in basic and clinical research and cooperates with research institutions in Ghana and Ruanda. One focus of research lies in the study of risk factors for malaria, e.g. genetics, pathogen properties, nutrition, poverty or other infections. Further topics are the effectiveness of new drugs and the development of resistance.

Hamburg: Bernhard-Nocht-Institute for Tropical Medicine²

The largest German institution for antimalarial research lies directly at the Hamburg Harbor. It is engaged in basic research of the various stages of the pathogen (liver and blood stage). In 2006 a team set a milestone and discovered a priorly unknown phase of the liver stage. It entered the textbooks as the "merosomen stage" (parasite-filled vesicles). Together with the Nanyang Technological University of Singapore, a database has recently been published which lists more than 2500 proteins from the pathogen *P. falciparum* and names their functions.³ This provides starting points for the development of new drugs. Together with the University of Kumasi, Ghana, genetic malaria resistance is studied, which occurs in regions with a large spread of malaria.

2007

Introduction of ASAQ fixed dose combination by DNDi

DNDi

Drugs for Neglected Diseases initiative
Asociativa Medicamentos para Enfermedades Olvidadas
Instituto Medicamentos para Doenças Negligenciadas

2007

The German Federal Chancellor Merkel promises an annual 200 million Euros for the Global Fund



Heidelberg

The Department for Infectious Diseases of the Heidelberg University Hospital⁴ studies certain metabolic mechanisms in order to find approaches for new drugs and to obtain knowledge of the formation of drug resistance. The Department for Infectious Diseases is connected to clinical research institutions in Africa.⁵ The Institute for Public Health has cooperated with Burkina Faso for years.

Munich

The Tropical Institute of the Munich University⁶ works in tight cooperation with hospitals in Tanzania and Ethiopia. In the Tanzanian Mbeya, resistant genetic mutations of the parasite are researched. Clinical studies on the therapy with ACTs are carried out together with the University of Jimma (Ethiopia). Malarial pathogens from Indonesia are used for researching new vaccines: so-called var-genes which are connected to the dangerous coagulation of the red blood cells occurring with severe malaria.

Tübingen

Tübingen has two institutions having decades of experience in tropical medicine: the university (Institute for Tropical Medicine)⁷ and the German Institute for Medical Mission (Deutsches Institut für Ärztliche Mission, Paul-Lechler-Krankenhaus).⁸ The Institute for Tropical Medicine studies the effectiveness of various antimalarial drugs and the preventive treatment of children.⁹ In cooperation with the Malaria Vaccine Initiative (see p. 23) there are clinical studies with the vaccine RTS,S. Research on a newly developed vaccine will soon

enter the clinical phase II; their partner is the African Malaria Network Trust.¹⁰ The most important research sites are the Albert-Schweitzer-Hospital Lambaréné in Central African Gabon¹¹ and in Sokodé, Togo.¹²

Würzburg

As one of few institutions worldwide, the University of Würzburg (Centre for Infectious Research) has an insectarium for the breeding of malaria-infected anopheles mosquitoes. They are used to carry out research for a vaccine which acts at the reproductive cells of the malarial pathogen.¹³ The Department of Tropical Medicine of the Medical Mission Hospital in Würzburg cooperated closely with hospitals in Zimbabwe, Somalia and Tanzania. At the Institute for Organic Chemistry, an international project studies the simultaneous treatment of malaria and HIV.¹⁴ (CW)

1 www.charite.de/tropenmedizin/Malaria.htm

2 www.bni-hamburg.de/

3 *Großangriff auf den Lebenszyklus von Malaria Parasiten (Major assault on the life cycle of malarial parasites).* Bernhard-Nocht-Institut, Pressemitteilung 8. Feb. 2010

4 www.klinikum.uni-heidelberg.de/Research.6567.o.html

5 www.klinikum.uni-heidelberg.de/SFB-544-Homepage.116129.o.html

6 www.klinikum.uni-muenchen.de/Abteilung-fuer-Infektions-und-Tropenmedizin/de/50_Forschung/Forschungsgruppen/AG_Malaria/index.html

7 www.medizin.uni-tuebingen.de/Zuweiser/Kliniken/Medizinische+Klinik/Tropenmedizin/Forschung.html

8 www.tropenlinik.de/

9 *Intermittent preventive treatment in infants* www.ipti-malaria.org

10 AMANET www.amanet-trust.org

11 www.lambarene.org

12 www.medizin.uni-tuebingen.de/feldforschung-parasitologie/AussenstationTogo.htm

13 www.zinf.uni-wuerzburg.de/zinf_research/pradel/

14 www.sfb630.de/

2008

Global Malaria Action Plan of the WHO



2010

Global Fund Replenishment Conference in New York



2015

Millennium Development Goal: malaria is curbed





13. “Only few people use bednets”

Interview with Djékadoum Ndilta about Malaria in Chad

Dr. Ndilta, you are working in the rural area of Chad?

Ndilta: Yes, our clinic is in a small village in the south of Chad. We are two medical doctors, working in a Christian hospital with 100 beds.

Is malaria a big problem?

Ndilta: Malaria is the main health problem in our country, followed by respiratory infections and diarrhea. Especially during the rainy season from June to November, the mosquitoes have excellent conditions to reproduce and many people get infected.

Who is mainly infected?

Ndilta: Children under 5 are suffering the most. And parents don't recognize malaria in each case. If their child has a fever, people wait saying “it will recover soon”. Or they buy some paracetamol on the market, which is bringing down the fever but not curing malaria. As a consequence malaria progresses, becomes severe or the child can die.

When do they go to see the doctor?

Ndilta: If the physical condition is becoming bad, people go to their

community health center. They get treatment with amodiaquin-artesunate tablets. It is only if the case is very serious and for example blood transfusion is needed, that they come to our hospital. In Chad you have to pay for your stay in hospital, so you go only if it is absolutely necessary. We also have many people from the North of Chad, to get treatment, not for malaria only but also for other diseases. Most of them come in groups using one car. They can sleep outside under the tree, and the other day they can go back home.

How is the prevention system working?

Ndilta: In theory, bednets are a good prevention. But in reality many people do not have bednets. Our research showed that only 38% of the population have bednets. And amongst those, only 15% use it.

Are bednets too expensive?

Ndilta: You know, 80% of the population are very poor. Many families have 6 or 7 children, and they hardly have any money. They have to wait until the end of the rainy season before they can sell their harvest on the market. If they get some money, buying bednets is not their priority.

What else can you do then?

Ndilta: We have an awareness raising program. Many women have no school education and no knowledge about malaria. So we started to send “health animators” to the villages. They tell people about Malaria, give worm treatment to children, and they give free bednets to the mothers.

Is the Chad government active?

Ndilta: In April 2010, the government introduced a new national malaria control program. Malaria medicines are free for children and pregnant women.

And if children are vaccinated, they get a free bednet.

Do you have problems with fake medicine?

Ndilta: Yes! Most of the drugs you can buy on the market come from Nigeria. These medicines are often of bad quality, containing no or insufficient active substances. This is one of the reasons why we have resistance against chloroquine. The artemisinin-based treatment is not available on the private market yet, so we have no resistance problems at the moment, but may have some in the future.

Interview: Christian Wagner-Ahlfs

About: Djékadoum Ndilta is a medical doctor training to become Master of Public Health. He is working at the Hôpital Evangélique de Koyom¹, a village in the South of Chad in Central Africa. Djékadoum Ndilta is active as a board member of the worldwide Ecumenical Pharmaceutical Network. Ndilta is cooperating with the DIFAM, running a mother-child health program.²

¹ www.tschadmission.org/fr/projets/travail-medical/hopital-evangelique-de-koyom/

² www.difaem.de/projekte/mutter-und-kind.html

Malaria is considered to be a tropical disease today. In earlier days, however, it also caused much suffering here in Europe. The marshes and moors of Northern Germany had been dreaded malaria-infested regions up to the 19th century. During the epidemic in 1826, every second child is said to have been infected with the marsh fever. Similarly, outbreaks of malaria were quite frequent at the Upper Rhine. Fortunately, this is a thing of the past. On the southern hemisphere though, malaria is still harsh reality even today. Almost one million people die of a fatal mosquito bite each year, every 30 seconds a child dies. That is reason enough to take a look at the disease.

This Pharma-Brief Special gives information on prevention, therapy and supply problems, provides the background on current research projects and describes the history of malaria between colonial politics and military interests.

BUKO

Pharma-Kampagne

BUKO Pharma-Kampagne
August-Bebel-Straße 62
33602 Bielefeld, Germany
Fon: +49 (0)521 60550
Fax: +49 (0)521 63789
Mail: info@bukopharma.de
Web: www.bukopharma.de

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