



Malaria

A Global Challenge



A Tanzanian village hospital

☐ Malaria

Malaria is one of the world's biggest killers. It infects up to 250 million and kills nearly 800,000 people per year. According to the World Health Organization (WHO) a child dies every 45 seconds as a result of the disease.

Malaria is a vector-borne disease caused by a single-celled protozoan parasite called *Plasmodium*, transmitted by female mosquitoes.

☐ History

Malaria is an ancient disease – written accounts of similar fevers first appeared around 6000BC. It was originally thought that malaria was contracted by breathing in bad air from stinking sulfurous marshes, hence the name *mal*, which means bad, in Italian, and *aria*, which means air.

Missionaries working in Peru in the early 1600s discovered that the powdered bark of the Cinchona tree could be successfully used to treat malaria. However, it wasn't until 1920 that two French chemists isolated the antimalarial compound quinine from the bark.

In 1880, Charles Louis Alphonse Laveran discovered that malaria was caused by *Plasmodium* while studying blood samples from soldiers with fevers.

He was awarded the Nobel Prize for Physiology or Medicine in 1907 for this work.

By 1898, 18 years later, Ronald Ross had not only worked out the life cycle of *Plasmodium* in the mosquito but had also proved, using bird malaria as a model, that only the female *Anopheles* mosquito transmitted malarial parasites. In 1902, he was awarded the Nobel Prize for Physiology or Medicine 'for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it'. Ross wrote 'the discovery was, perhaps, as really important as the discovery of America' as now managing the spread of the mosquito could help to control the spread of malaria.



Cinchona bark



Ronald Ross (left) and Charles Louis Alphonse Laveran (right)

□ Epidemiology

Malaria was successfully eliminated from countries with temperate climates during the mid-20th century, using public health measures; however, it is still found throughout the tropics and subtropics of Africa, Asia, and South America. After a decline in malaria cases up to 1970, incidence increased until 2005; this was due to one or more of the following factors:

- ▶ an increase in the spread of resistance to antimalarial drugs and insecticides;
- ▶ widespread poverty and an inadequate availability of good healthcare systems in malaria endemic countries;
- ▶ increased global air travel and migration, and conflicts which may have helped the spread or re-intensification of the disease;
- ▶ and, new breeding sites for mosquitoes due to environmental changes caused by humans.

According to the *WHO World Malaria Report 2010*, since 2005 increased finance available for insecticide-treated mosquito nets and indoor residual spraying has produced measurable impacts on public health; there has been a decline in malaria cases from 244 million in 2005 to 225 million in 2009. The number of

countries with endemic malaria is also declining, with Morocco and Turkmenistan the latest to be registered as free from malaria in 2010; this leaves 100 malaria-endemic countries at the time of writing.

□ At risk

Most of those dying from malaria are children, as they have not developed natural immunity to the disease; in Africa malaria kills 1 in 5 children. Another high-risk group is pregnant women because of natural changes in the immune system during pregnancy which make infection more likely. Malaria in pregnancy can lead to premature babies, low birth weight and generally less-healthy babies. Those travelling to areas of the world where malaria may be prevalent are also at risk, as they will not have developed immunity to it.

□ Reduced risk

People with sickle-cell anaemia, a genetic disorder, are less likely to contract malaria and tend to survive in areas where the disease is widespread. This is because their haemoglobin, the oxygen-carrying part of the red blood cell (RBC), is defective. Consequently, these individuals have a low binding capacity for oxygen and are 50% less efficient at



An indoor residual spraying team in a village in northern Nigeria

carrying it. The *Plasmodium* parasite has an active aerobic metabolism and is unable to thrive in conditions of reduced oxygen availability. People who are susceptible to developing systemic lupus erythematosus, an autoimmune disease which leads to tissue damage, also receive protection against the malaria parasite because their white blood cells (WBCs) and other components of the immune system are able to clear malaria parasites more efficiently.

▣ What causes malaria?

Five species of the single-celled protozoan parasite *Plasmodium* can cause malaria in humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. knowlesi* and *P. malariae*. Of these, *P. falciparum*, the dominant species in Africa, is the deadliest and is responsible for approximately 90% of malaria deaths per year. However, it has been estimated that more people worldwide live at risk from *P. vivax* than *P. falciparum* and as a result suffer increased morbidity from *P. vivax*. Each species of the *Plasmodium*



parasite differs in phenotype, immune response, geographical distribution, relapse pattern and drug response.

Malaria is a vector-borne disease transmitted from one person to another by certain species of blood-sucking mosquitoes of the *Anopheles* genus which includes *A. gambiae* – the primary vector for transmission of *P. falciparum* malaria in sub-Saharan Africa.



Female mosquitoes transmit malaria as they feed on blood; they need the high levels of proteins in the blood meal to develop their eggs. They are attracted to humans by smell and vision. Slender, sharp, saw-toothed stylets on the end of the female mosquito's proboscis pierce the skin and probe for a suitable small blood vessel. While sucking up the blood, the mosquito pumps saliva into the host. Chemicals in the saliva prevent the blood from clotting and act as an anaesthetic to stop the host feeling the mosquito while it is feeding. The characteristic red, itchy swelling of a mosquito bite is due to an allergic reaction to the left over saliva.

Male mosquitoes do not transmit the disease as they feed only on plant juices.

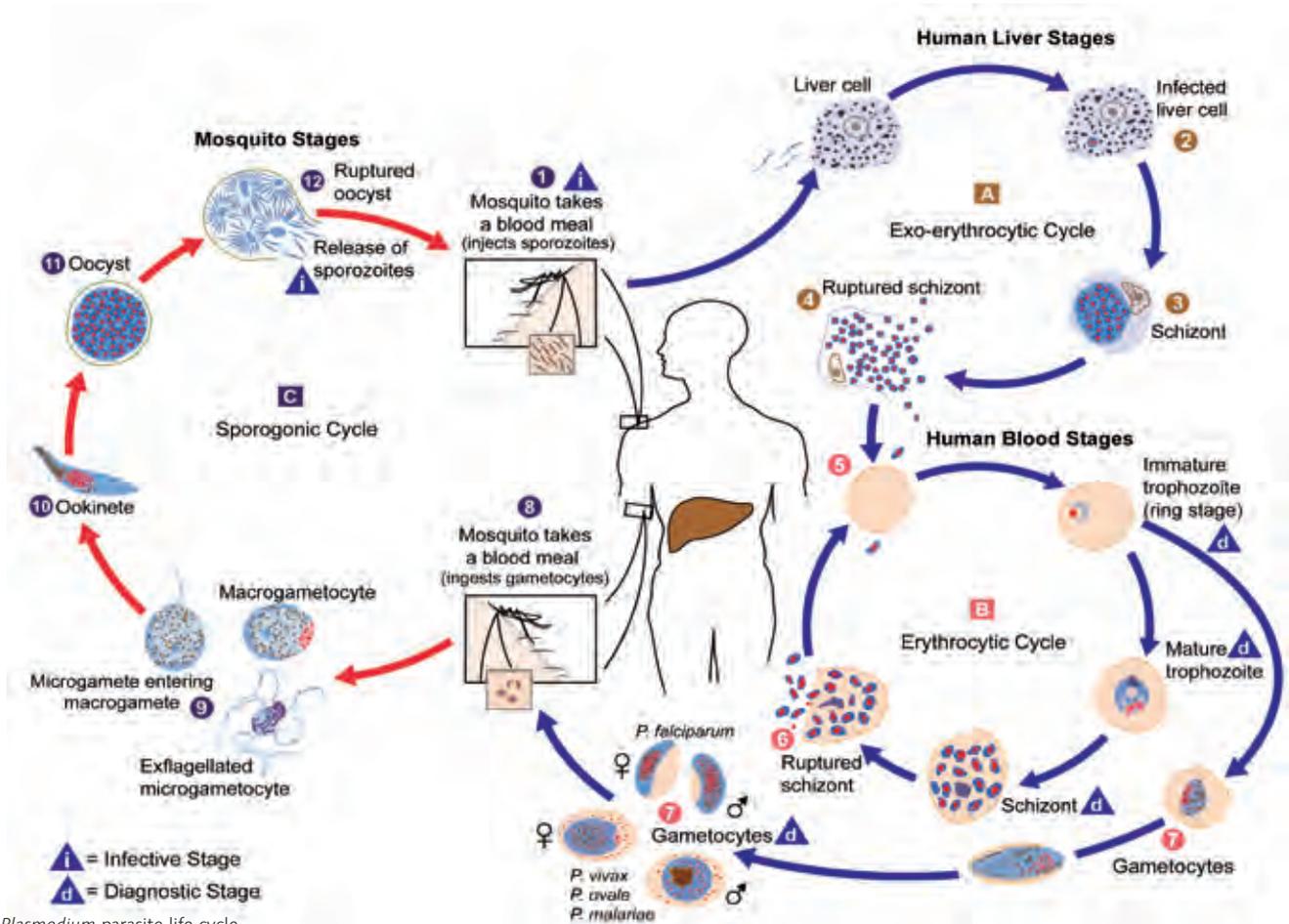
▣ How is malaria spread?

The *Plasmodium* parasite has a complex life cycle characterized by alternating extracellular and intracellular forms, involving sexual reproduction in the mosquito and asexual reproduction in the liver cells and RBCs of humans (see diagram).

The parasite enters the human host when an infected mosquito takes a blood meal **1**.

Sporozoites from the mosquito's salivary glands are injected into the host's bloodstream. Within 30 minutes the sporozoites will have entered the host's liver cells **2**. The sporozoites feed on the cell contents, grow and change to form schizonts **3**. Over the next 5–8 days they divide rapidly, forming thousands of merozoites. The liver cells balloon and burst **5**, releasing merozoites into the bloodstream where they invade the RBCs.

While the parasite is within the liver the person does not feel sick and shows no signs or symptoms



The Plasmodium parasite life cycle

of the disease. *P. vivax* and *P. ovale* can have a dormant stage in the liver called hypnozoites. These can remain in the liver for several years, causing relapses in later life.

While in the liver and the RBCs the parasite is protected from the host's antibodies.

Inside the RBCs the individual merozoites develop into trophozoites and finally into schizonts (6) which contain up to 32 distinct merozoites, depending



Coloured transmission electron micrograph of a section through red blood cells infected with the malaria parasite

upon the species of *Plasmodium*. After 2–3 days the RBCs rupture, releasing the merozoites back into the bloodstream. These merozoites go on to invade uninfected RBCs and the cycle continues (B). As the RBC ruptures toxins are released from the merozoites. It is believed that these toxins directly stimulate the host's immune system and a highly complex immune response is initiated, resulting in bouts of chills, fever and sweats. In *P. vivax malaria* this can occur once every 48 hours, corresponding to the RBC cycle.

Some of the trophozoites develop into male and female gametocytes (7), the sexual stages of the parasite. These circulate in the blood and are taken up by the female mosquito when it takes a blood meal (8). Inside the mosquito's stomach the gametocytes develop into gametes, fertilization occurs and a zygote is formed. Within 24 hours the zygotes transform into motile ookinetes (10) that burrow into the stomach wall. Ookinetes encyst and become oocysts (11) that divide to produce approximately 1,000 sporozoites each. After about 7 days the oocysts rupture, releasing their sporozoites

12, which make their way to the salivary glands ready to infect another human.

☐ Mosquito (vector) life cycle

The female mosquito is able to lay her eggs on almost any type of standing or slow-flowing water, breeding in temporary puddles such as hoof prints and tyre ruts, shallow natural ponds, marshes, irrigation ditches and water tanks. The laying sites are dependent upon the species of mosquito. The female lays between 100 and 300 eggs at a time. It takes 1–5 days for the eggs to hatch. After the eggs have hatched into larvae they feed on micro-organisms present in the water. The larvae then develop into non-feeding pupae; during this stage the adult insect is formed. The cycle takes 7–21 days, depending on the ambient temperature.

☐ Symptoms & diagnosis

Malaria is diagnosed by clinical symptoms, microscopic examination of the blood or rapid diagnostic tests (RDTs). RDTs use blood from a pin-prick to identify infection based on the presence of antigens.

Fever, headache, chills and vomiting – the classic flu-like symptoms of malaria – appear around 9–14 days after the initial mosquito bite. The time differs according to the species of *Plasmodium*. The WHO currently recommends that all cases of suspected malaria should be confirmed before treatment commences, while treatment on the basis of 'clinical suspicion' should only be permitted when parasitological diagnosis is not available. Currently,



Young girl with a rapid diagnostic test



Large-scale examination of blood smears, part of the Sri Lanka malaria eradication programme

approximately 35% of cases in Africa are confirmed using an RDT.

Malaria may lead to anaemia and jaundice because RBCs are destroyed faster than they can be replaced; severe anaemia is the leading cause of death in children with malaria.

Blood transfusions can be used to treat anaemia, but in areas where AIDS is endemic this exposes the patient to the risk of infection with HIV.

Cerebral malaria may arise after infection with *P. falciparum*. It is characterized by coma and convulsions, and often results in death. 10–20% of children with cerebral malaria die and around 7% of those that survive are left permanently brain-damaged.

There are two main theories relating to the cause of cerebral malaria.

- ▶ **Mechanical:** Knob-like projections appear on the surface membrane of the infected RBCs. These are sticky and can either adhere to non-infected RBCs, forming clumps, or to endothelial cells lining the surface of blood vessels. Blockages in capillaries can result, causing a reduction in blood flow and tissue damage. This is extremely serious when it occurs in vessels supplying the brain.

▶ Immune response: Cytokines, which are released in response to toxins from ruptured RBCs, induce the production of the gas nitric oxide. It is generally believed that nitric oxide can diffuse through the blood–brain barrier and act as a general anaesthetic, causing the patient to lapse into unconsciousness and coma. However, scientists reported in *The Lancet* in 2002 that African children carrying a single genetic mutation which caused their cells to increase the production of nitric oxide were protected from developing cerebral malaria. It is thought that nitric oxide may prevent the RBCs from sticking to blood vessels, therefore maintaining blood flow to the brain.

▣ Prevention & control

There is no single way to prevent malaria. Currently, it is controlled by a combination of mosquito management and physical barriers, which both aim to prevent mosquito bites, along with intermittent preventative treatment (IPT). These approaches aim to reduce the intensity of transmission of the disease.



▶ Mosquito management & physical barriers

Vector control remains one of the most generally effective methods to prevent malaria transmission. The two main lines of defence are the use of indoor residual spraying (IRS) (mosquito management) and insecticide-treated nets (ITNs) (physical barriers). These interventions may be complemented by additional strategies.

- ▷ IRS involves spraying the internal surfaces of a dwelling with insecticides to target areas where the mosquitoes rest after taking a blood meal. While this approach is incredibly effective, disapproval of the chemical DDT has resulted in a decline in its use. Depending upon the insecticide used, insecticide spraying is effective for 3–6 months, or 9–12 months in the case of DDT.
- ▷ ITNs are mosquito nets impregnated with pyrethroids, a class of insecticide. It is recommended that they are retreated with insecticide at least once per year. Long-lasting insecticidal nets are favoured by the WHO; these are designed to be effective for at least 3 years, removing the need for regular insecticide treatment. A chemical halo that extends away from the nets is produced by the insecticide. Many malaria-endemic countries in Africa make ITNs freely available to people at risk of malaria.
- ▷ Breeding site reduction/environment management strategies modify the local environment preventing the larvae having access to suitable breeding conditions for example, covering or removing water containers, filling in ditches or effective drainage.
- ▷ Biological control methods introduce natural enemies to help manage mosquito populations, for example, parasites and pathogenic, or predatory,



Bacillus sphaericus: a bacterium used as a biological control agent to kill the larvae of specific mosquitoes



A health worker in Brazil spraying a drain with *Bacillus sphaericus* bacteria to kill mosquito larvae

organisms such as insects, viruses, bacteria, protozoa, fungi, nematode worms, plants or fish. Of these methods the use of larvae-eating fish and bacteria, for example, *Bacillus thuringiensis* or *Bacillus sphaericus* which produce protein crystals that are highly toxic to the mosquito larvae, are the only methods widely employed.

Most mosquitoes bite between dusk and dawn. To reduce the risk of being bitten at night, long-sleeved tops and trousers should be worn and insect repellent applied to the skin.

► IPT

IPT with doses of the drug sulfadoxine/pyrimethamine is recommended for vulnerable populations such as pregnant women and infants in areas where transmission is high. In pregnant women, IPT reduces the risk of maternal anaemia, placental parasitaemia and low birth weight; by 2010 it had been adopted as a national policy for pregnant women across 39 of 47 sub-Saharan African countries. IPT is now being integrated into the malaria control programmes of a number of African countries for infants, though none have declared a national policy so far.

▣ Malaria eradication

Several attempts have been made to eradicate malaria. In 1955, the WHO launched the Malaria Eradication Campaign which succeeded in eradicating malaria in Europe, the former USSR, most of North America, several Middle Eastern countries, large parts of South America, the Caribbean, Japan, Australia, Taiwan and Singapore. The campaign was abandoned in 1969 somewhat short of its goals, as malaria persists in Latin America, most of Asia and Africa. The WHO now fronts a campaign of malaria control. In recent years, however, interest in global malaria eradication has intensified.

▣ Treatment

Malaria can normally be treated with antimalarial drugs. The type of drugs and length of treatment depend on which kind of malaria is diagnosed, where the patient was infected, the age of the patient and how ill the patient was at the start of the treatment. Travellers visiting endemic areas can take antimalarial drugs to prevent infection. Depending upon the drug prescribed, they may need to be taken up to 2 weeks before travelling, during the period the person is away and for 4 weeks afterwards to be effective.

Artemisinin-based combination therapies (ACTs) are now the standard treatment for uncomplicated malaria. These therapies combine artemisinin or one of its derivatives with another antimalarial or antimalarials of a different class.



Antimalarial drugs from *Artemisia annua*

Current recommended drugs for ACT are:

- ▶ Artemether-lumefantrine
- ▶ Artesunate-mefloquine
- ▶ Artesunate-amodiaquine
- ▶ Artesunate-sulfadoxine/pyrimethamine
- ▶ Dihydroartemisinin-piperaquine

Uncomplicated malaria is defined as '*a symptomatic infection with malaria parasites in the blood without signs of severity and/or evidence of organ failure or dysfunction*'. The choice of ACT depends on its efficacy in the geographical area of use. Combinations of antimalarial drugs can be given as separate tablets at the same time or as a co-formulation into a single tablet. ACT therapy can slow the onset of resistance as the antimalarials used in combinations have different mechanisms of action. This means that if a mutant parasite resistant to one of the drugs arises during the course of the infection the other drug will still kill the resistant parasite.



Artemisia annua

▶ Artemisinin and its derivatives

Extracted from the Chinese plant *Artemisia annua*, artemisinin and its derivatives are effective for both treating malaria and reducing its transmission. The drugs act rapidly on the parasites reducing those present in the blood drastically. They act 10 times more quickly than the next best antimalarial, quinine. They reduce transmissibility, as they are able to destroy gametocytes present in the blood. Artemisinin derivatives are not recommended as monotherapies because of the possible emergence of drug resistance. When used in combination, artemisinin (or derivatives) eliminates the majority of the parasites and quickly leaves the body; the combination drug, for example mefloquine, then mops up the remaining parasites.

P. vivax malaria is treated with chloroquine. However, in areas where resistance has developed an ACT is advised; a 14-day course of another drug, primaquine, is also recommended in addition to ACT to prevent relapse.

In cases of severe *P. falciparum* malaria, drugs are administered by intramuscular or intravenous injection of quinine followed by a complete course of an effective ACT as soon as the patient is able to take oral medication. In situations where injections are not feasible, patients can be treated with artemisinin suppositories.

▶ Emergence of drug resistance

The malaria problem is getting worse because the mosquitoes that transmit the disease are becoming resistant to insecticides (for example, those used for spraying the walls of houses or to impregnate nets) and the parasites are becoming resistant to the drugs used to treat them. South-east Asia has the most resistant malarial parasites in the world.

In Africa the increase in drug resistance to chloroquine and sulfadoxine/pyrimethamine is believed to be directly responsible for large increases in the number of deaths from malaria and hospital admissions for severe malaria. This is because if malaria sufferers are treated with failing drugs, the infection is prolonged and the number of RBCs destroyed by the parasite is increased, which in turn leads to anaemia.

In light of the developing resistance to current antimalarial drugs, the WHO recommends thorough

monitoring of the effectiveness of any malaria treatment and prevention regime in order to follow and adapt to changes.

▶ Counterfeit drugs

The distribution of counterfeit and substandard antimalarial drugs is spreading. The availability of these drugs jeopardizes the lives of the individuals who are given them but also potentially fuels drug resistance. Help is needed in malaria-endemic zones to identify and remove these products from the market.

▶ Vaccines

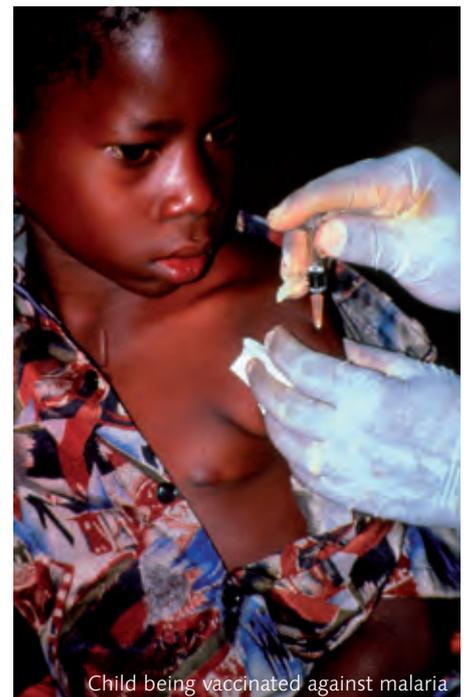
Vaccines are the most effective way of controlling infectious disease; however, there is currently no vaccine against malaria. Developing an effective vaccine is proving to be very difficult because of the complexity of the *Plasmodium* life cycle in the host. It is hoped that one day two distinct vaccines will be developed, the first aimed at reducing severe malaria in pre-exposed individuals such as those living in endemic areas, and the second being available to travellers.

For a vaccine to be 100% effective against the liver stage it must kill all the parasites within the infected liver cells so that none emerge to infect the RBCs. It is thought by some researchers that the most effective vaccine will target the parasite at each stage of its life cycle:

- ▷ Sporozoites (antibodies)
- ▷ Liver stage (T cell-mediated)
- ▷ Blood stage
- ▷ Transmission

The majority of vaccines work by stimulating the body's WBCs to produce antibodies against the disease. This only works when

the invading micro-organism is in extracellular fluid or blood but not when it is inside the cells of the host, as the antibodies cannot penetrate them. The *Plasmodium* parasite spends most of its life cycle in the host's liver cells and RBCs, and is only extracellular for a limited time at the sporozoite and merozoite stages. Late-stage clinical testing (Stage III clinical trial) of the candidate vaccine RTS,S produced by GlaxoSmithKline, began in May 2009. The vaccine is made of a protein from the surface of the *P. falciparum* sporozoite and a surface antigen from the hepatitis B virus. It is targeted to the pre-erythrocytic (RBC) stages of *P. falciparum* malaria and is designed to stimulate the production of antibodies and T cells which reduces the ability of the parasite to infect, survive and develop in the liver. By using the hepatitis B antigen the vaccine is targeted to liver cells and provides protection against hepatitis B which factors heavily in the development of liver disease and liver cancer. The trial is showing good results so far. Based on these results, scientists have continued to optimize the vaccine



Child being vaccinated against malaria

by altering dosage, formulation and delivery schedules, and further clinical trials are now underway across Africa. Subject to the results of further trials the vaccine could be submitted to the regulatory authorities in 2011, with a vaccine available as early as 2013; this would be aimed at children in malaria-endemic areas.

While this vaccine currently does not offer the complete protection delivered by vaccines for other diseases, the drastic reduction in infection rates will relieve at least some of the burden of the disease.

Latest research

In 2002, the entire genomes of *P. falciparum* and *A. gambiae* were published. Coupled with the publication of the human genome in 2000, this is helping scientists to develop new strategies to treat malaria, such as vaccines and vector control. The rapidly decreasing cost and greatly increased speed of sequencing of complete genomes from many genetically variant strains of the parasite is currently providing much new information.

Research has intensified over recent years to create a mosquito which is unable to transmit the malaria parasite. Scientists working at the University of Arizona have engineered *Anopheles stephensi*

mosquitoes which are immune to the parasite; *A. stephensi* is prevalent in the Middle East and South Asia areas. It is closely related to *A. gambiae* and is frequently used in laboratories across Europe. It is hoped that one day these mosquitoes will replace the natural populations in the wild.

Scientists have discovered a new type of preventative treatment against malaria. The treatment is an antibiotic (clindamycine or azithromycine) that, when administered to mice at the same time as they are infected with malaria, protects against the development of parasites in the blood. Treatment in this manner also generates a long-term immunity against the parasite. This treatment is very encouraging and could potentially be administered at regular intervals as a needle-free 'natural' vaccination. However, this work is still in its infancy and further testing is necessary in order to 'scale-up' to reflect human infection.



World Malaria Day

April 25 is World Malaria Day - a day to promote or learn about the efforts being made globally to combat this deadly disease. The WHO, the United Nations, government organizations, charities, communities and individuals play a role by putting on events and activities to raise awareness of the disease. What will you do?



Further Information

- ▶ World Health Organization – www.who.int/topics/malaria/en/
- ▶ Wellcome Trust Malaria at a Glance – <http://malaria.wellcome.ac.uk/node40029.html>
- ▶ Roll Back Malaria – www.rollbackmalaria.org/
- ▶ World Malaria Day – www.worldmaliaday.org/home_en.cfm
- ▶ Net Doctor – www.netdoctor.co.uk/travel/diseases/malaria_disease.htm
- ▶ Malaria World – www.malariaworld.org/

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Acknowledgements

Thanks are due to **Professor John Hyde (The University of Manchester)** and **Dr Annemieke van Eijk (Liverpool School of Tropical Medicine)** for their helpful comments on this text. Every care has been taken to ensure that the information is correct, but the author will be pleased to learn of any errors that have remained undetected.

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