

# Developing Treatments



## Malaria

Malaria is a life-threatening parasitic disease. When a female *Anopheles* mosquito bites a human, she can pass on one of four species of *Plasmodium* parasite, which all cause malaria. The typical symptoms are bouts of fever and chills. In more serious cases, usually caused by the *Plasmodium falciparum* parasite, infected red blood cells can clump together and block blood flow. At worst, the disease can damage internal organs, including the brain, and cause breathing difficulties, coma and death.



Approaches to malaria have always been two-fold – preventing someone from catching the disease (prophylaxis) and treating them if they catch it.

## Ague and Fever

'Malaria' means 'bad air' in Italian. The word was first used in Britain in the 1800s. Before, people used 'ague', 'marsh fever' or 'intermittent fever' to describe malaria-type illnesses.



This cartoon by Thomas Rowlandson was published on 29<sup>th</sup> March 1788. It shows a patient sitting in front of a fire trying to keep warm, while Ague, a snaky monster, clings to him. Fever, a furry monster, stalks the room.

## Malaria in Britain

It is very difficult to be sure when malaria first appeared in Britain. From the 1400s onwards, malaria was common in the Fenlands of East Anglia. It was also common in the marshes and along the coasts and estuaries of south-east and northern England. International traders from the 1500s onwards introduced the disease from abroad. In the 1600s, Westminster and Lambeth were amongst the places in London that were well-known for endemic malaria.

### Local remedies

People in the Fenlands used opium from locally-grown poppies and pubs served beer containing opium. Another popular cure in the 1600s was bathing your legs in hot milk, or drinking "carduus posset", a hot drink made from thistles.

The Countess of Kent was prescribed the following medicine for malaria in 1653:

*"Take the inner bark of a Walnut tree, a good quantity, boyl it in beer until the beer looks black, and then take a good draught and put it in a pot, then take six spoonfuls of Sallet (salad) Oyle for an extreme Ague, brew it too and fro in two pots, then drinke it."*

Leonard Sowerby recommended "A spider bruised in a cloth, spread upon linnen and applied to the fore-head or Temples" for 'tertian ague' in 1652:

Mary Doggett suggested the following cure for the ague, published in 1682:

*"Take feverfew and sage and bruise them with half a pennyworth of Pepper. One little spoonful of Chinny (chimney) Soot and ye white of an egg mingle them together and lay it to ye wrist."*

## Quinine



Quinine has had the biggest impact on reducing the number of deaths from malaria. It is the active plant ingredient from the South American cinchona tree.

### Peruvian bark

The Countess of Chincón, the wife of the Viceroy of Peru in the 1630s, gave her name to cinchona. She was supposed to have been cured of a fatal fever with a secret remedy containing a bark from a tree in the Loxa region. She then supplied it to the poor and

the sick, who named it "the Countess's Powder." We know now that this is a myth, but the name cinchona stuck. Apparently, the name is "cinchona" rather than "chincona" because the botanist Linnaeus made a spelling mistake when he classified the plant in 1742!

The name "quinine" comes from the native Peruvian word for cinchona bark, "kina". European Jesuit missionaries in Peru became aware of its anti-malarial properties in the 1600s. It became known in England as "Peruvian bark" or "Jesuit's bark."

## Quinine in Britain

Cinchona was introduced into Europe by the 1630s. In 1667, "Peruvian bark" was added to the London Pharmacopoeia for the first time.



### ***Cinchona officinalis*, lithograph by Walter Hood Fitch.**

Fitch was Kew's principal artist from 1837 to 1877, and produced more than 10,000 botanical illustrations in this time.

The famous physician Thomas Sydenham (1624-1689) recommended Peruvian bark for malaria, but it was very expensive.

### **Robert Talbor**

Robert Talbor, an English apothecary's apprentice, pioneered the use of cinchona in malaria treatments. He first used his secret remedy in the Fens and Essex. When his cure was given to King Charles II and members of the European royalty, Talbor received a knighthood and was made Royal Physician. The King of France revealed that cinchona was the significant ingredient in Talbor's remedy, after Talbor's death in 1681.

John Quincy in his *A Compleat English Dispensatory* of 1718 was less sure about the new medicinal ingredient:

*'This comes to us from Peru in the West – Indies; whence the Romish Missionaries first brought it into Europe, and gave occasion for its being call'd Jesuits Bark. This Simple is so lately brought into Medicine, that there is little to be met with in Authors about it; and People's Notions seem yet so confus'd and undetermin'd concerning its Virtues and Efficacy...'*

## Meeting the Demand

The alkaloid (active plant ingredient) quinine was first extracted from the bark of cinchona trees by two French chemists, Pierre Joseph Pelletier and Joseph Biename Caventou in 1820. By the late 1800s, quinine was the main treatment for malaria.

To meet the massive demand for cinchona in the 1800s, Dutch and English explorers and entrepreneurs collected seeds in South America to establish plantations in India, Sri Lanka and Java.

### **Manuel Incra Mamani**

Charles Ledger was one of the pioneering English explorers. Between the 1840s and 1870s, he successfully worked with the local Bolivian guide Manuel Incra Mamani to find cinchona seeds. In 1865, Charles' brother, George Ledger visited Robert Bentley, Professor of Botany at the Pharmaceutical Society, and gave him some seeds. Bentley put Ledger in touch with J.E.Howard, a quinine manufacturer in Tottenham, north London. Howard was the first to appreciate the seeds' commercial potential. He put Ledger in contact with Dutch experts.

Dutch plantations in Java planted with Ledger's seeds produced trees richer in quinine than any known so far, and transformed the cinchona industry.

### **John Eliot Howard**

J.E.Howard (1807-1883) was the leading "quinologist" in the second half of the 1800s. He was central to the establishment of cinchona plantations in India. His collection of cinchona specimens were donated to the Society's Museum. Some examples include:

#### ***Cinchona condaminea* from Ecuador**

This sample is labelled "*The knotty sort of Jussieu*" in Howard's handwriting. Joseph de Jussieu was a pioneering French botanist who explored Colombia and Peru in the 1730s to build up knowledge and a collection of specimens of cinchona.

#### ***Cinchona lancifolia* from New Granada, now Colombia**

Howard labelled this 'Orange Bark of Mutis.' Jose Celestino Mutis was a Spanish physician and botanist who built up a vast knowledge of cinchona through living and travelling in New Granada (now Colombia) from 1761 until his death in 1808.



This photograph is labelled 'Santiago Son of Manuel, Faithful Attendant Senor Don Carlos Ledger', and dates from around 1860

#### ***Cinchona calisaya* from Bolivia**

From the 1700s onwards, this species of cinchona was believed to be the most effective source of quinine. Clements Markham led a British expedition in 1860 to collect *Cinchona calisaya* plants. His aim was to establish a plantation in India, but none of his seedlings survived in the British government plantations.

### **Howard's quinine preparations**

John Howard was born into an important pharmaceutical family. The family firm, Howard's, was a very successful manufacturer of fine chemicals. Quinine was its most profitable product in the 1800s. They continued to make anti-malarial medicines into the twentieth century, alongside many other preparations.

## Cinchona plantations



View of San Carlos cinchona plantation, Bolivia, with the proprietor Senor Don Manuel Calderon, 20 December 1882. Calderon was a friend of Charles Ledger.

View of cinchona plants in the propagating house at the Government gardens Ootacamund, Madras, India, 9<sup>th</sup> September 1891. These British government gardens became a major centre for producing cinchona in the second half of the 1800s.



## Quinine-based Medicines

### Anti-malarial treatments

This group of quinine-based anti-malarial medicines all date from the twentieth century.



- Quinine sulphate was used in large doses for malaria, and in smaller doses for other fevers, neuralgia and as a tonic to improve the appetite.
- Quinine bisulphate or acid quinine sulphate is a more soluble form of quinine.
- Quinine hydrochloride was used as an antiseptic earwash and a pessary, and was injected for malaria.

- Tincture of quinine was given when small doses were needed to treat or prevent malaria.
- Quinine hydrochloride acidum was for hypodermic use for malaria, ague, rheumatism and typhoid fever.

**Photograph above shows:**

Dr Albutt's quinine injection powder.  
 Iron and Quinine citrate, from Parke, Davis & Co. medicine case.  
 Quinine sulphate B.P., Unichem, 1970s.  
 Quinine sulphate B.P. 1958, British Drug Houses.  
 Quinine sulphate, Arthur H. Cox & Co Ltd.  
 Quinine dihydrochloride, Arthur H. Cox & Co Ltd.  
 Quinine sulphate, British Drug Houses.  
 Quinine bisulphate, from Parke, Davis & Co. medicine case.  
 Quinine bisulphate 'Tabloids', Burroughs Wellcome, mid-20<sup>th</sup> century.  
 Quinine (Quininae sulphas B.P), Boots the Chemists, mid-20<sup>th</sup> century.

Quinine is still used as the first-line treatment for the most serious type of malaria, caused by the *Plasmodium falciparum* parasite.

**Other quinine-based medicines**

Quinine was also used to treat fevers, headaches, neuralgia, influenzal catarrh, and as a general tonic.

**Photograph shows:**

Quinine tooth powder, Cooper's Dentifrice Depot.  
 Pepper's quinine and iron tonic, strengthening agent, around 1915.  
 Cobden's quinine and phosphorus pills.  
 Dr Flemming's quinine and camphor pills.  
 Dandelion and quinine bilious and liver pills, International Chemical Co.Ltd, for bile, wind and indigestion and stomach afflictions, early 20<sup>th</sup> century.  
 Anadin, which contained aspirin and quinine sulphate, International Chemical Co.Ltd., for headache, rheumatic pain, cold and 'flu.  
 Ac.Acetylsal. et Quinin.Co (Compound aspirin and quinine tablets), Willows, Francis, Butler and Thompson Ltd.  
 Ammoniated tincture of quinine B.P.C., Boots Pure Drug Co.Ltd., for colds and 'flu.



**Understanding the Disease**

Charles-Louis-Alphonse Laveran was the first person to identify the presence of the malaria parasite in human blood. Having spent four years as Associate Professor of Epidemic Medicine at the French army's medical school, he was posted to Bone in Algeria in 1878. He faced cases of malaria every day, and began to carry out research. He took material from autopsies, and fresh blood from patients. However, it took him four years after his discovery in 1880 to persuade other scientists that he was right.

### Ronald Ross

Ronald Ross won Britain's first Nobel Prize for Medicine in 1902 for his research into malaria. He carried out practical experiments with mosquitoes and patients whilst working for the Indian Medical Service. Through these he discovered that the disease is spread by the transfer of malaria parasites through a mosquito's bite.



### Treating Malaria in the Twentieth Century

By the 1930s, the parasites that cause malaria were becoming resistant to quinine. Other medicines were developed to treat malaria.

#### *Photograph shows:*

**Mepacrine**, mid-20<sup>th</sup> century.  
Mepacrine was developed by scientists at Imperial Chemicals Ltd in 1939 and was used in World War Two. It is no longer used for malaria.

**"Methylene Blue"**, mid-20<sup>th</sup> century.  
Methylene Blue (methylthiomine chloride) was first recommended to treat malaria, and other conditions, in the 1890s. Unfortunately, its side-effect was to turn the patient's urine and faeces bright blue. This example was produced by British



Drug Houses. Scientists are still investigating its continued use as an anti-malarial.

#### **Atovoquone**, 2005.

Atovoquone is one of the most popular current anti-malarial drugs for Western travellers. It became available in 1997, as Malarone, in combination with proguanil. Users seem to suffer from less side-effects, and it needs to be taken for a shorter period of time than other current treatments. However, the manufacture of atovoquone is extremely expensive and so the highly effective treatment is limited to the prevention of the disease for affluent tourists.

## Malaria, Empire and War

Malaria was a significant risk to Westerners living, working and fighting in tropical or water-logged areas. Keeping soldiers fit for service meant that armies had to take the prevention and treatment of malaria very seriously. In the twentieth century, new conflicts also prompted the development of new malaria treatments.

### Exploration and empire

#### Keeping well in the tropics

By the early 1800s, chemists and druggists were supplying medicine chests with contents specially chosen for people living in the tropics.



This chest, sold by Savory and Moore, dates from the early 20<sup>th</sup> century. It includes quinine bisulphate to treat malaria.

#### Tonic water, modern.

Tonic water was developed by army officers in India in the mid-1800s. They added sugar to the quinine dose that they were taking to prevent malaria to make it more palatable, and added a little gin. This led to gin and tonic as we know it today. Schweppes launched its Indian Tonic Water in the 1870s. It still contains quinine.

#### Tabloid quinine, early 20<sup>th</sup> century.

The famous explorer, Henry Stanley met with Henry Wellcome in the 1880s. As a result, Burroughs Wellcome established a medicine chest department. They subsequently supplied lightweight cases, filled with their "tabloid" preparations, to many travellers and explorers. This case made by Burroughs Wellcome includes quinine tablets.



#### Livingstone rousers

While Stanley's medicine chest contained "Zambesi rousers" as an anti-malarial, David Livingstone, the discoverer of the Zambezi River and Victoria Falls, had a "rouser" named after him. "Livingstone rousers" contained quinine acid sulphate, jalap, calomel and rhubarb.





### **Army supplies, circa 1910.**

This 'Pill and Tablet Tin' was designed and supplied by Burroughs Wellcome. The supplies include two bottles of quinine hydrochloridum acidum Tabloid brand tablets. The Indian Army Ordnance Corps Depot mark on base of bottles shows that that the tin was still in use by the Indian Army after Indian independence in 1947.

### **World War One**

"You paraded for quinine once or twice a day. You went in front of the Sergeant Major who was in charge of the quinine powder. You'd put your tongue out, he'd have a little spoon and would dig into this can of quinine and place a small spoonful on the tip of your tongue. Then you'd be ordered to drink from your mug of water and swallow."

Private Francis Ching. XVI Corps Cyclists.



**"British troops taking their daily dose of quinine powder, Struma Valley, summer 1916."**

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### **Salonika Campaign**

The British Army established a base in Salonika, northern Greece, in October 1915. By October 1918, there had been 162,000 cases of malaria in a force of 160,000 men. However, effective treatment with quinine limited the number of deaths to 821. The Salonika Campaign Association today still takes the mosquito as its emblem.

## World War Two

During the Second World War, supplies of German medicines were interrupted. This included pamaquine (Plasmaquin) – first marketed in 1926 - and mepacrine (Atebrin).

When the conflict extended from Europe to the Far East, this exposed the troops to malaria, and also cut off the route to Java, which was the main source of quinine. Luckily, this problem had been foreseen, and projects began to synthesise new antimalarial drugs in 1941. These culminated in the development of proguanil and chloroquine.

### Paludrine, circa 1970s-1980s.

Proguanil (Paludrine) was developed by scientists at ICI in the 1945. They aimed to find a more effective anti-malarial drug than quinine or mepacrine.

### Chloroquine

Chloroquine was first synthesised by German scientists in the 1930s. It was fully developed by Winthrop in 1946. It has been the most common treatment for malaria since the 1950s. Although it is still a safe, inexpensive and widely available drug, resistance to it now occurs across the tropical world, so it is no longer effective in many areas.



### The Vietnam War

Mefloquine (Lariam) was developed by scientists in the US Army. It was first used to treat troops fighting in the Vietnam War in 1971. Antimalarial treatment with mefloquine was initially very successful. However, because the parasites became resistant to the drug, by the mid-1990s, failure rates had reached 50%.

Although effective, mefloquine is a controversial treatment, as some people experience side-effects such as dizziness, nightmares or even serious neuropsychiatric reactions.

### Photograph above shows:

Paludrine (Proguanil), Imperial Chemicals (Pharmaceuticals) Ltd., 1970s/1980s

Nivaquine (Chloroquine sulphate), May and Baker Ltd., 1940s

Avloclor (Chloroquine diphosphate), Imperial Chemicals (Pharmaceuticals) Ltd., 1940s/1950s

Lariam (Mefloquine), Roche Products Ltd, 2005.

## Malaria Today

According to the World Health Organisation, more than 1 million people, mainly in sub-Saharan Africa, are killed in the world each year by malaria. More children die from malaria each year than from measles and HIV/AIDS combined. There is currently no vaccine for malaria.

Malaria has become an international priority. Existing methods of prevention and treatment of malaria could be greatly improved with increased resources. However, new approaches for prevention and treatment are also needed.

Since the 1950s, locally-transmitted malaria has virtually died out in Britain. However, the

number of imported cases has grown with the increase of overseas travel. The average number of malaria cases in the 1970s was around 200 each year. Now it's around 1,500.

One important measure is to stop mosquitoes biting people in the first place. The development of long-lasting bed nets in which insecticide is incorporated into the net fibres now provide a simple but effective means of preventing malaria. There is also a huge range of insect repellent products on sale.



### Recent Research

The Vietnam War prompted Chinese researchers to develop new anti-malarial drugs. Their most important discovery was qinghaosu, or artemisinin, from the plant *Artemisia annua*. (sweet wormwood). Scientists are currently evaluating the effectiveness of artemisinin drugs combined with other anti-malarial medicines in Africa and South America. One artemisinin-based treatment is Riamet (lumefantrine and artemether), launched in the UK in 2002. A World Health Organisation report in 2005 stressed that new anti-malarial drugs must be used in combination with other medicines, to weaken the ability of the disease's parasite to become resistant.

Scientists have now sequenced the malaria parasite genome. This information is helping researchers to develop new anti-malarial drugs. This is very important, as the parasite that causes the disease is very quick to develop resistance to antimalarial drugs.

Several new drugs are under development. One malaria vaccine, RTS,S/AS02, has shown promise in endemic areas and will shortly enter further trials. Other vaccines are being studied in clinical trials, but it will probably be at least 10 years before a malaria vaccine is ready for widespread use.

Mosquito-killing fungi are currently being tested by researchers as a new approach. They have found two different fungi that seem to kill mosquitoes, but are safe for people – an ideal combination.

Another approach has been pioneered by British scientists, who have created mosquitoes with glowing testicles. The male mosquitoes can then be easily identified and sterilised, which should reduce the size of the mosquito population.