MALARIA FOUNDATION INTERNATIONAL

FACT PACK
Archived Information from 12 August 1997

This information was gathered in 1997 by the Malaria Foundation International with contributions from over 30 international experts.

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1. Scale

- Around 2.5 billion people (at least 40% of the world's population) are at risk in over 90 countries

- Malaria causes or contributes to 3 million deaths and up to 500 million acute clinical cases each year. In other words:

- Almost as many deaths per annum as the AIDS death total in the last 15 years

- 20 times more deaths each day than deaths from the 1995 EBOLA epidemic in Zaire (~250).

- Cause of more military casualties than bullets in every 20th century war in malarious regions

- The majority of deaths are children. In other words children are dying at a rate of 4 per minute, 5,000 a day and 35,000 a week.

- Other high risk groups include pregnant women, refugees, migrant workers, and non-immune travellers - over 20 million Western tourists at risk annually.

- The main areas affected are Africa, South East Asia, India and South America but surveillance and records are too poor to know the real distribution and case numbers.

- Malaria is one of leading causes of morbidity and mortality in the developing world (along with TB, acute respiratory syndrome, diarrhoea and HIV) but still not recognised in developed countries as a disaster like AIDS or EBOLA.

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2. Spread

Malaria kills more people today than three decades ago. Reasons for the spread include:

- Increasing drug resistance
- Increased migration and immigration
- Increase in size of endemic territories (e.g. people moving from countryside to cities)
- Tourist and business travel (increased air travel since 1950s/60s)
- Decreased mosquito control efforts (insecticide spraying)
- Deforestation and mining (development activities)
- WHO predicts an extra 80 million cases of malaria annually by the end of the 20th Century -i.e. a 16% increase within 3 years.
- Malaria is spreading to new territories for example, India, Brazil, Sri Lanka, Turkey, and the Middle East.
- Malaria is spreading from the countryside into cities (e.g. Bombay/Mumbai), increasing the risk for city dwellers and tourists in these ‘safe’ zones of endemic countries.
- International travel is increasing and travellers are increasingly at risk, especially given the difficulty in ensuring proper prevention by systematic drug intake.
- Climatic conditions and increased immigration means that malaria could spread to the West (e.g. Florida) within 10 years. There have been recent reported cases in Florida, New Jersey, California, Georgia, Michigan, New York and Texas. Historical precedents for Northern malaria include:
- US - endemic from colonial times to early 20th century
- Cases as far north as Siberia and Canada up to the 1950s
- Paris epidemic in the 1940s due to local mosquitoes infected via troops from Africa
- Widespread indigenous cases around the Mediterranean up to the 1960s
- 30 years ago malaria had been eradicated or dramatically reduced in 37 countries (WHO insecticide spraying programme 1956-69) but this situation has been rapidly reversing, especially over the last decade. The reversal is largely due to the cost of sustaining programmes, loss of motivation in the face of a seemingly declining threat, and the development of insecticide and drug resistance.
- India’s malaria eradication programme in the 1950/60s reduced infections from 75 million to 100,000 per annum and fatalities from 800,000 to almost none. Over the past two decades, the trend has reversed with four major epidemics since 1994. In 1996, 2.85 million cases were reported, and the official - and under-reported - death toll was around 3,000.
- In 1960 malaria was practically eradicated in Azerbaijan but by 1995 reported cases reached almost 3,000 across two-thirds of the country. The main cause is the recent influx of refugees into the endemic South.

- *Plasmodium vivax,* the classically 'benign' malaria (which has been known to make people very sick but not kill them), is now believed by some experts to be potentially lethal in cases involving drug resistant parasites. In 1994, *P.vivax* was reported resistant to chloroquine in several Indian cities and districts.

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3. Cost

- Malaria exacts an enormous toll in lives, medical costs and days of labour lost. Educational systems also suffer as large numbers of children miss several weeks of school each year in endemic regions.

- The direct annual commercial loss in Africa due to malaria is currently estimated to be US $1.8 billion a year. In 1987 the figure stood at US $800 million. If this trend continues, the cost is likely to reach US $3.6 billion by 2000 (US $10 million a day).

- A single bout of malaria is estimated to cost a sum equivalent to 10-20 working days in India and Africa.

- India will spend US $40 million on malaria control in 1997 - up 60 per cent from last year. It is also planning a five year programme targeting 210 million people in 100 high risk districts that account for 80 per cent of all potentially fatal cases in India. This US $215 million programme will be funded primarily by a World Bank loan.

- The average cost of current treatment per dose ranges from US $0.08 and US $10.00 depending on the type of drug.

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4. Obstacles to Remedial Action

Political commitment

- Insufficient political commitment for improved health services

- Inadequate surveillance and control programmes

- Insufficient international public funding

- Inadequate training/career opportunities for local malaria scientists/health professionals

Resistance

- Drug resistance is increasing rapidly, largely due to widespread uncontrolled and unregulated drug distribution.

- Drugs have been used until resistance has rendered them ineffective, after which closely related drugs that are introduced show reduced efficacy and severely compromised life spans.

- Today, there are few effective anti-malarial drugs - most tropical countries still rely on chloroquine (which is increasingly ineffective) primarily due to cost and the limitation of alternatives.

- The vicious circle of new drug resistance limits research and rollout options and increases the cost of R&D - it is hard to establish whether to use new options widely, risking resistance, or keep them in reserve until resistance to existing drugs such as chloroquine or quinine becomes widespread.

- Another underlying factor contributing to the development of resistance is the improper usage of the drugs; for example, subcurative doses - people feel better, so stop taking their medicine, and some resistant parasites may be given the chance to survive and be transmitted by mosquitoes.

- There is insufficient research into novel drug targets. Current new options are based on the same three families of compounds (the quinolines, antifolates, and artemesinin derivatives) all of which have records of resistance and/or ineffectiveness.

- Insecticide programmes have also been hampered by the emergence of resistance to DDT and other insecticides.

Vaccine development problems

- Parasites have a more complex structure than viruses and bacteria and change appearance over the course of an infection. Finding the best way to attack them via vaccination is not easy - further research on their composition and biology is needed even before addressing major issues such as how to produce and administer a vaccine.

- The two main malaria parasite species are sufficiently different from each other that a vaccine based on one will probably not prevent malaria by the other.

Gaps in essential research

- Biochemistry of the parasite

- Basis of parasite drug resistance

- How people build up immunity to malaria

- Transmission characteristics and epidemiology (differs throughout the world)

- Pathogenesis (i.e. development characteristics of malaria)

- Mosquito biology, infection, genetics, insecticide resistance

- Effect of malaria on other diseases and vice versa

- Environmental factors

Inadequate international co-ordination of research efforts

Some progress has been made over the last decade but there is still a growing need for multi-lateral initiatives to co-ordinate research, training and control efforts. Recent actions include:

1991 - "Malaria: Obstacles and Opportunities" published; A report of the Committee for the Study on Malaria Prevention and Control: Status Review and Alternative Strategies Division of International Health; Institute of Medicine, USA. Important committee recommendations put forward.

1992 - Ministerial Conference on Malaria in Amsterdam (WHO and Dutch sponsored): Ministers of health adopted a Global Malaria Control Strategy. The World Health Assembly, The Economic and Social Council of the UN General Assembly and the United Nations (UN) General Assembly subsequently endorsed the Strategy. Its goals are to promote early diagnosis and treatment, ward off epidemics and engage communities in mosquito control programmes. This has led to Action Plans in a number of African countries and, more recently, the Harare Declaration (see below).

1993 - Regional Task Force for Malaria Control in Africa (Established by WHO/AFRO with US AID [Agency for International Development] Support)

1996 - Malaria Research Worldwide; An Audit of International Activity (Wellcome Trust sponsored audit; publication available): Determination that only $ US 84 million is spent annually on malaria worldwide. This is extremely low considering the scope of this problem and the number of people, families, and communities severely affected.

1997 - "The Year for Malaria": major turnaround in outlook for this disease; strong renewed interest; optimism for continued momentum and scientific breakthrough.

January 1997 - International Conference on Malaria: Challenges and Opportunities for Collaboration in Africa; Dakar, Senegal: Ground work laid for Multilateral Initiative on Malaria (MIM), which became official in July, and an appeal to the international community to mobilise in the fight against malaria (Nature, Vol 386, page 541)

February 1997 - A Meeting of Experts on Malaria Control Initiative in Africa; Brazzaville, Congo: WHO/AFRO meeting to develop initiatives to accelerate the implementation of malaria control in Africa.

June 1997 - Harare Declaration on Malaria Prevention and Control in the Context of African Economic Recovery and Development (by the Heads of State and Government of the Organisation of African Unity); Harare, Zimbabwe: Proposed plan of action and budgetary needs published.

June 1997 - Malaria Genome Consortium meeting; Cambridge; England: Progress and increased commitment to malaria DNA sequencing and analysis efforts demonstrated by the leading funders and scientists involved in this research.

July 1997 - Multilateral Initiative on Malaria (MIM; The Hague, The Netherlands: a strong coalition of several of the world's major research agencies, medical charities and donor agencies, which have joined forces to explore ways forward in the fight against malaria. Began in Dakar, Senegal in January and officially took root in The Hague, The Netherlands in July. One immediate goal of the MIM is to greatly improve the global networking and research capabilities of scientists. The other major goal is to facilitate research developments (and hopefully breakthroughs) via new and regular multilateral partnerships and collaborations. A follow-up meeting will be held in England in six months time.

August 1997 - The Ronald Ross Centenary Malaria Meeting (The Second Global Meet on Parasitic Diseases - with emphasis on malaria); Hyderabad, India; August 18-22, 1997. This meeting, in large orchestrated by the MFI, is a very strong demonstration of the commitment of scientists and public health officials to malaria research and control. Over 100 of the world’s leading malaria scientists are scheduled to speak and over 650 people are registered to attend. Goals of the meeting include the strengthening of scientist co-operation aimed at reviving public and funding agencies interest in this forgotten disease.

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5. Investment in Research

Global expenditure on research per associated death for various diseases

Diseases	Annual global research ($ million)	Global mortality (1990: Thousands)	Estimated global research expenditure per fatal case worldwide (1990)
HIV/Aids	952	290.8	3274
Malaria	**60**	**926.4**	**65**

- Limited national and international research budgets - US $84 million spent on malaria research in 1993 versus US $2.3 billion per annum for cancer, US $1.5 billion on AIDS, US $300 million on Alzheimer’s.

- The USA is the largest single country contributor to malaria research (US $35 million in 1994) but its budgets have declined over the past decade. It is now increasing its support. The National Institute of Allergy and Infectious Diseases of the National Institute of Health (NIH/NIAID) is the leading sponsor.

- Europe as a block invests at least as much as the US. The European Commission has become one of the leading supporters of research in partnership with developing country scientists.

- Total malaria expenditure in the UK has been increasing over the past decade, from approximately US $4 million in 1985 to approximately US $15 million in 1994. The Wellcome Trust has been a major sponsor of malaria research, primarily in the UK and Africa.

- In Asia, the Thai government is leading a five year US $12.5 million research programme (40% National Science & Technology Development Agency, 40% the Thailand Research Fund and 20% funding from the WHO’s Tropical Disease Research Programme).

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6. Infection Basics

- There are four species of human malaria parasites but only two are highly prevalent: *Plasmodium falciparum* and *Plasmodium vivax*

- *P. falciparum,* the major cause of malaria deaths, accounts for around 90% of African malaria and about 50% in South East Asia/Latin America.

- *P. falciparum* may exist in blood at low non-clinical levels (due to partially effective immunity or incomplete drug treatment) and then increase to cause obvious illness.

- *P. vivax* can lie dormant in the liver and relapse up to several years after the initial illness. Cause of relapse "trigger" is unknown.

Carriers of Infection

- All human malaria is spread by female 'Anopheline' mosquitoes which need a supply of blood in order to produce and lay eggs.

- These mosquitoes become infected by taking blood from an infected individual.

- Malaria can also be transmitted by blood transfusion, contaminated needles and syringes and in rare cases, from mother to child before and/or during birth.

How human malaria infections occur

- The malaria parasite reproduces inside the infected mosquito forming a sac with thousands of new malaria parasites. (Development of the parasite inside the mosquito is influenced by the outside temperature).

- In order to infect an individual, the infected mosquito has to live 15 days at which point the parasites burst out of their sac and reach the salivary glands of the mosquito.

- As a mosquito bites it injects infected saliva.

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7. Malaria cycle

There are three main stages:

Stage I: Upon infection by the mosquito, the malaria parasites move rapidly into the liver - within ~30 minutes - and reproduce there rapidly for 5 days or more, depending on the species (*P. falciparum* or *P. vivax)*.

Stage II: The malaria parasite breaks out from the liver, enter the bloodstream, and within minutes invade red blood cells, where they grow and divide. Every 48-72 hours (time differences depend on the species) the red blood cells rupture, dispersing more parasites along with waste products/toxins into the blood stream. This step causes fever, chills and anaemia in the victim - telltale clinical signs of malaria. The released parasites then invade other red blood cells, beginning the cycle again.

If untreated, the malaria disease can progress causing a variety of serious complications. Most seriously, *P.falciparum* parasites cause blockage of blood vessels; cerebral malaria, coma and death can ensue. For sufferers without partial immunity (e.g. Western travellers, migrant workers), it is possible for death to occur in only 24 hours after the first appearance of symptoms.

P.vivax does not adhere to blood vessels and cause the associated complications; however, unlike *P.falicparum*, dormant *P.vivax* can burst out of the liver into the bloodstream months or several years later ready to start the vicious clinical cycle again.

Even if not fatal, malaria infection can potentially make a person vulnerable to death from other causes.

Stage III: Some parasites invade red blood cells and develop into sexual forms that are ingested by uninfected biting mosquitoes, within which they mate and begin to reproduce. These parasites make their way to the salivary glands of the mosquito, ready to move on to another victim when the mosquito takes its next blood meal.

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8. Treatments

- *Quinine,* a natural product from the bark of the Cinchona tree, was one of the first treatments for malaria and appeared in the 17th Century. It is still effective but can be toxic. *Quinine* remained drug of choice for treatment and prevention until 1942 when chloroquine took over. With widespread chloroquine resistance, *quinine* together with artemether have become the two major and best available treatments today - for any type of malaria. In countries where quinine resistance is developing, it is used in combination with other therapies such as tetracyclines and clindamycin.

- *Chloroquine* was first used in the 1940s and is a weekly course. Today it is manufactured by all the major pharmaceutical companies. The first cases of resistance were found in South America and South East Asia in the early 60's and is now ineffective almost everywhere. However it is still the widest used anti-malarial (mainly in Africa) as it is the cheapest drug available; in some countries only less than US $0.10 per tablet.

- *Sulfadoxone/pyrimethamine (Fansidar SP)* was developed in the 1960s. The course comprises three doses taken together on one day. Today, this drug is manufactured by a number of pharmaceutical companies, although the *Fansidar* trademark belongs to Hoffman LaRoche. Despite widespread resistance in South East Asia and parts of South America, it is starting to become the first line of treatment in some African countries where chloroquine resistance has been widespread. Malawi and Kenya have made an official commitment to using Fansidar but others are reluctant to follow due to perceived increased cost and/or logistics problems encountered in trying to introduce change into their health systems. Generic SP may cost as little as US $0.11 per tablet.

- *Mefloquine (Lariam)* was developed by the US army in the early 1980s and commercialised by Hoffman LaRoche. Resistance has been observed since the early 1980s particularly on the Thai/Cambodia and Thai/Burmese borders (50% resistance). Some people have reported some side-effects such as dizziness and nausea.

- *Halofantrine* was also developed by the US army and marketed by SmithKline Beecham in the 1990s. Cross-resistance with mefloquine and side-effects (sometimes severe) have been observed. At US $ 10.00 the treatment is relatively expensive and impractical for public health use.

- *Artemisinins* (derived from ancient Chinese herbal remedy) comprise a family of products. The two compounds most widely used are artemether and artesunate, mainly in Southeast Asia but not widely used in the developed world in part due to toxicity fears, licensing and logistic issues. More research data is needed for these products to meet international standards. Due to the high rate of treatment failures, artemisinins are now being combined with mefloquine. As such, they are very effective. Artemisinins are manufactured by both the Chinese and Vietnamese State Manufacturing Units, as well as several companies.

- All the above are treatments for *P. falciparum* or *P. vivax* malaria cases. P*rimaquine* is the only treatment available for eliminating the dormant forms of *P. vivax* which remain in the liver. Resistance to primaquine has been noted in the past few years.

Future treatment possibilities

There is an urgent need for the development of new drugs based on new compounds. In the meantime, combination therapies based on current drugs are being tested which include:

Licensed

- *Azythromicine* - a doxycycline replacement for children and pregnant women.

- *Malarone* (Glaxo Wellcome*;* atovaquone/proguanil HCl*)* gained its first license in October 1996. Licenses are being sought worldwide. Clinical studies are ongoing.

- *Arteether* - License imminent

In later stages of clinical development

- *Co-Artemether* (Novartis; Benflumetol/Artemether*).*

- New generation 8-aminoquinolines for curative treatment of *P.vivax*, possible replacement for primaquine (From India, CDRI 80/53, and from the US Army, WR238605)

Other

- Novel associations such as cycloguanil-dapsone (similar to what Fansidar is made of)

- *Pyronaridine* - evaluated in China and being reassessed by WHO but proven effective in limited treatment of African patients.

- Chloroquine analogues and combination therapies

Although, the above compounds are in different stages of testing and clinical trials, it is important to note that none have the promise, as well as the combination of ease of use, efficacy, and low cost that chloroquine had when it first came on the scene as a "wonder drug" in the 1940's.

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9. Preventatives

Drugs

- Prophylactic recommendations vary according to the preference of different countries and also individual doctors. The majority recommend Mefloquine (Lariam) for non-immune travellers, a weekly treatment. It is approximately 90% effective. However, some people have reported side effects**,** among them dizziness and nausea.

Vaccines

- No vaccine yet available for use. Increased R&D is needed for vaccine development.

- An experimental vaccine candidate against the infectious mosquito stages is currently undergoing Phase III Clinical trials led by SmithKline Beecham Biologicals (SBBIO).

- Additional peptide and DNA vaccine candidates are being tested in early Phase I clinical trials.

- Other potential vaccine candidates need to be explored further for each stage of the malaria infection.

Other

- Protection against mosquito bites using skin repellents, mosquito nets etc can help, when feasible.

- Addressing environmental, development and educational issues/perspectives can help to immediately reduce morbidity and mortality.

Insecticide Treated Bed Nets (ITBN)

- The WHO Tropical Disease Newsletter (Jan 1997) suggested that the lives of some 500,000 young African children might be saved every year from malaria if bednets, treated with biodegradable pyrethroid insecticide, were widely and properly used. Because they are treated with insecticide they not only prevent mosquitoes from attacking victims but also kill the mosquitoes.

- A 1991 study in the Gambia (West Africa) showed a 63% reduction in childhood mortality using ITBNs. A second study in The Gambia revealed a 25% reduction in all-cause child mortality. More recently (1996) in Kilifi, Kenya, under very different epidemiological and cultural conditions deaths were cut by a third.

- However, it is possible that the initial reduction of mortality may not be sustainable. Longer term studies on ITBN effectiveness need to be undertaken.

- ITBNs are costly and uncomfortable in the hot and humid tropics so their practicality must also be evaluated. Alternatives such as insecticide impregnated curtains are also being considered.

Insecticide Treated Bed Nets (ITBN)

Country	**% reduction in all-cause child mortality**	**Project Organizer**
The Gambia	63	Medical Research Council Laboratories, The Gambia
The Gambia	25	Gambian National Bednet Impregnation Programme
Kenya	33	WHO organized trials
Ghana	17	WHO organized trials

10. Brief 100 year History on Anti-malarials

circa. 1880	Laveran discovers malaria parasite
20 August 1897	**Sir Ronald Ross reveals the complex development of the malarial parasite in the mosquito. Quinine was drug of choice at this time**
1932	Mietzsch, Mauss and Kikuth report synthesis of new anti-malarial - a yellow acridine dye - Atabrine
1940's	Further research into synthetic anti-malarials prompted by malaria outbreaks among British and US troops during World War II
1941	Synthesization of Atabrine on a commercial scale in the US. Widespread use among Allied forces
1940’s	Development of two 4-aminoquinoline compounds in Germany - Sontochin and Resochin
	Following further trials, Resochin is ultimately chosen drug and is renamed chloroquine
	ICI study the potential of pyrimidine derivatives as anti-malarials
1945	Curd, Davey and Rose identify proguanil (Paludrine) as a drug with low toxicity and high activity against avian malaria
1951	Further studies of pyrimidine derivatives lead to development of pyrimethamine (Daraprim) by Hitchings and other scientists of the Burroughs Wellcome Company in the US
1950’s	Effectiveness of proguanil and pyrimethamine towards *P. falciparum* infections found to be declining
1960	Resistance to chloroquine identified in Colombia with other countries soon to follow
1990's	*See above*