Chapter IV

MALARIA RESEARCH: AN OVERVIEW

4.1. INTRODUCTION

Malaria is a disease caused by a parasite* that lives part of its life in humans and part in mosquitoes. Malaria remains one of the major killers of humans worldwide, threatening the lives of more than one-third of the world’s population. It thrives in the tropical areas of Asia, Africa, and Central and South America, where it strikes millions of people. Each year 350 to 500 million cases of malaria occur worldwide. Sadly, more than 1 million of its victims, mostly young children, die yearly.

Malaria imposes great socio-economic burden on humanity, and with six other diseases (diarrhea, HIV/AIDS, tuberculosis, measles, hepatitis B, and pneumonia), accounts for 85% of global infectious disease burden.\(^1\,^2\) Malaria afflicts more than 90 countries and territories in the tropical and subtropical regions, and almost one half of them are in Africa, South of Sahara. About 36% of the world population (i.e., 2020 million) is exposed to the risk of contracting malaria. The World Health Organization estimates 300-500 million malaria cases annually, with 90% of this burden being in Africa. In addition, the estimated annual mortality attributed to malaria ranges from 700,000 to 2.7 million globally.
and > 75% of them are African children and expectant mothers. Doubts have been expressed about reliability of these estimates because most of the hyper- and holoendemic countries, especially in Africa, lack credible diagnostic facilities and reporting systems.³

4.2. MALARIA

Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a type of unicellular microorganism) of the genus Plasmodium. Commonly, the disease is transmitted via a bite from an infected female Anopheles mosquito, which introduces the organisms from its saliva into a person's circulatory system. In the blood, the protists travel to the liver to mature and reproduce. Malaria causes symptoms that typically include fever and headache, which in severe cases can progress to coma or death. The disease is widespread in tropical and subtropical regions in a broad band around the equator, including much of Sub-Saharan Africa, Asia, and the Americas.

Malaria has been around since ancient times. The early Egyptians wrote about it on papyrus, and the famous Greek physician Hippocrates described it in detail. It devastated invaders of the Roman Empire. In ancient Rome, as in other temperate climates, malaria lurked in marshes and swamps. People blamed the unhealthiness in these areas on rot and decay that wafted out on the foul air.
Hence, the name is derived from the Italian, "mal aria," or bad air. In 1880, the French scientist Alphonse Laveran discovered the real cause of malaria, the single-celled *Plasmodium* parasite. Almost 20 years later, scientists working in India and Italy discovered that *Anopheles* mosquitoes are responsible for transmitting malaria.

Historically, the United States is no stranger to the tragedy of malaria. This disease, then commonly known as “fever and ague,” took a toll on early settlers. Historians believe that the incidence of malaria in this country peaked around 1875, but they estimate that by 1914 more than 600,000 new cases still occurred every year.

Malaria has been a significant factor in virtually all of the military campaigns involving the United States. In World War II and the Vietnam War, more personnel time was lost due to malaria than to bullets.

The discovery that malaria was transmitted by mosquitoes unleashed a flurry of ambitious public.

### 4.3. ORIGIN AND HISTORY

Human malaria likely originated in Africa and has co-evolved along with its hosts, mosquitoes and non-human primates. The first evidence of malaria parasites was found in mosquitoes preserved in amber from the Palaeogene period that are
approximately 30 million years old.[2] Malaria may have been a human pathogen for the entire history of the species.[3][4] Humans may have originally caught Plasmodium falciparum from gorillas.[5] About 10,000 years ago malaria started having a major impact on human survival which coincides with the start of agriculture (Neolithic revolution); a consequence was natural selection for sickle-cell disease, thalassaemias, glucose-6-phosphate dehydrogenase deficiency, ovalocytosis, elliptocytosis and loss of the Gerbich antigen (glycophorin C) and the Duffy antigen on the erythrocytes because such blood disorders confer a selective advantage against malaria infection (balancing selection).[6] The three major types of inherited genetic resistance (sickle-cell disease, thalassaemias, and glucose-6-phosphate dehydrogenase deficiency) were present in the Mediterranean world by the time of the Roman Empire, about 2000 years ago.[7]

References to the unique periodic fevers of malaria are found throughout recorded history.[9] According to legend, the Chinese emperor Huang Di (Yellow Emperor, 2697–2590 BCE) ordered the compilation of a canon of internal medicine. The Chinese HuangdiNeijing (The Inner Canon of the Yellow Emperor) apparently refers to repeated paroxysmal fevers associated with enlarged spleens and a tendency to epidemic occurrence – the earliest written report of malaria.[10] The presence of malaria in Egypt from circa 800 BC onwards has been confirmed using DNA based methodologies.[11] The term 'miasma' was coined by Hippocrates
of Kos who used it to describe dangerous fumes from the ground that are transported by winds and can cause serious illnesses. The name malaria derived from ‘mal’aria’ (bad air in Medieval Italian). This idea came from the Ancient Romans who thought that this disease came from the horrible fumes from the swamps. The word malaria has its roots in the miasma theory, as described by historian and chancellor of Florence Leonardo Bruni in his HistoriaFlorentina, which was the first major example of Renaissance historical writing:[12].

4.4. HOW INFECTED WITH MALARIA

Malaria is transmitted through the bite of an infected, female Anopheles mosquito and occasionally through blood transfusion. When a mosquito bites a person it sucks up blood. If the person has malaria, some of the parasites in the blood will be sucked into the mosquito. The malaria parasites multiply and develop in the mosquito. After 10-14 days they are mature and ready to be passed on to someone else. If the mosquito now bites a healthy person, the malaria parasites enter the body of the healthy person. The parasites are transported in the bloodstream to the victim's liver where they multiply and then re-enter the bloodstream.

The malaria parasites can multiply 10 times every 2 days, destroying red blood cells and infecting new cells throughout the body.
4.5. TYPES OF MALARIA

Malaria is caused by protozoan parasites of the genus

- *Plasmodium* – single-celled organisms that cannot survive outside of their host(s).

- *Plasmodium falciparum* is responsible for the majority of malaria deaths globally and is the most prevalent species in sub-Saharan Africa. The remaining species are not typically as life threatening as *P. falciparum*.

- *Plasmodium vivax* is the second most significant species and is prevalent in Southeast Asia and Latin America. *P. vivax and Plasmodium ovale* have the added complication of a dormant liver stage, which can be reactivated in the absence of a mosquito bite, leading to clinical symptoms.

- *P. ovale* and *Plasmodium malariae* represent only a small percentage of infections.

- A fifth species *Plasmodium knowlesi* – a species that infects primates – has led to human malaria, but the exact mode of transmission remains unclear.

Malaria has been known for hundreds of years and poses a threat across several continents. According to experts, nearly 300 million to 500 million people suffer from malaria each year and almost 2 million die – mostly children younger than 5 years and most of them in Africa. The deaths caused by malaria each year are more than from any other infectious disease except AIDS and tuberculosis.
(TB). After the launch of malaria eradication program in different countries, the incidence of malaria and death rate due to it dropped considerably during the 1960s. However, it emerged with a renewed vengeance during the later decades. Two main reasons responsible for the resurgence of malaria are insecticide-resistant mosquitoes and drug-resistant parasites, besides the emergence of wild varieties of vectors like *Anopheles dirus* and *Anopheles minimus*, increased international air traffic, administrative lapses and poor financial support.

4.5.1. Uncomplicated Malaria

Children and adults infected with malaria commonly suffer from high fever and severe aches but symptoms may also include cough and diarrhoea. Any child who presents with fever in a malaria endemic region or who recently visited such a region, must be assumed to have malaria until proven otherwise, and requires urgent treatment. The most important feature of malaria is fever. Early diagnosis and treatment will save lives and prevent the development of complications. All parents and caregivers should be made aware of malaria symptoms and urged to seek prompt treatment.

4.5.2. Severe or Complicated Malaria

Untreated malaria in a young child or in a non-immune individual may become complicated: the patient presents with very high body temperature,
drowsiness, convulsions and coma indicating heavy parasitaemia and cerebral malaria. Other complications may include bleeding, jaundice, diminished urine output, all signifying liver and/or kidney failure.

Each attack may last several hours and often begins with shivering (body shaking). Next, there is a period of fever, and finally there is profuse sweating. During an attack, the patient often complains of headache and pain in the back, joints and all over the body. There may also be loss of appetite, vomiting and diarrhoea. Alternatively, the child may present with symptoms of severe malaria such as loss of consciousness, drowsiness and/or convulsions, diarrhoea, dark urine and reduced urine output (anuria).

If untreated (or inadequately treated), malaria may cause several weeks or months of poor health because of repeated attacks of fever, anaemia and general weakness. Malaria symptoms can mimic many illnesses and can affect mostorgans in the body.

It is particularly important to make an early diagnosis of malaria in young children and in pregnant women. These two groups may rapidly become very ill and may die within a few days. Pregnancy reduces the immune status of individuals and hence makes them more susceptible to malaria infection. Malaria
during pregnancy is more difficult to treat, because the parasites tend to hide in the placenta, making diagnosis and treatment difficult.

4.5.3. How to Recognize Malaria

It is difficult to tell whether a sickness is caused by malaria or some other disease, because the features may be similar. Ask the patient, or the adult accompanying a young patient, whether there has been any fever at any time during the past 2-3 days. The patient has a fever when the forehead feels hot, or more precisely when his or her temperature is more than 37.5 degrees centigrade on a thermometer. Very young children with malaria may present with low body temperatures or hypothermia. Patients who have had fever during the last 2-3 days may have malaria. In this case, ask and then look for danger signs.

4.5.4. Danger Signs of Severe Malaria

Look for the following signs of malaria, and ask the following questions to each patient, or parent or care-giver

- accompanying a child:
- if he/she is able to drink
- if he/she has had fever at home
- if he/she has had convulsions (fits)
- does he/she vomit repeatedly or have diarrhoea or a cough
• how much urine he/she has passed – very little, none at all? Is it dark or blood coloured?

4.5.5. Look for:

• changes in behaviour (convulsions (fits); unconsciousness; sleepiness; confusion; inability to walk, sit, speak or recognize relatives).

• repeated vomiting; inability to retain oral medication; inability to eat or to drink

• passage of small quantities of urine or no urine, or passage of dark urine severe diarrhoea

• unexplained heavy bleeding from nose, gums, or other sites

• high fever (above 39 degrees centigrade)

• severe dehydration (loose skin and sunken eyes)

• anaemia (look at the patient’s facial colour and hands – the palms of a patient with anaemia

• do not have the redness of a healthy person’s palms)

• yellowness of the eyes.

4.6. MALARIA BETWEEN 1990 AND 2000

With the worsening of the malaria situation worldwide, new international initiatives, such as the 'Multilateral Initiative on Malaria' (MIM), and 'Roll Back
Malaria' (RBM) were launched during the late 1990s. MIM7, a coalition of organizations and individuals, was initiated in 1997 with the objective to strengthen and sustain, through collaborative research and training, the capability of malaria-endemic countries in Africa to carry out the research required to develop and improve tools for malaria control. RBM8, a program of the World Health Organization (WHO) launched in 1998, is a multisector partnership that works with malaria-endemic countries to develop and implement prevention and treatment programs. The goal of RBM is to cut the global malaria burden to half by 2010.

4.7. MALARIA INCIDENCE IN INDIA

In India, the epidemiology of malaria is complex because of geo-ecological diversity, multiethnicity, and wide distribution of nine anopheline vectors transmitting three Plasmodial species: *P. falciparum*, *P. vivax*, and *P. malariae*. *Anopheles culicifacies* is widely distributed and is the principal vector of rural malaria, *An. stephensi* is the primary urban vector, *An. fluviatilis* is a vector in the hills and foothills, and *An. minimus, An. nivipes, An. philippinensis*, and *An. dirus* are vectors in the northeast and *An. sundaicus* is restricted to Andaman and Car Nicobar islands. *An. annularis* and *An. varuna* are secondary vectors with wide distribution.
4.8. PERSONAL PROTECTION AND SELECTIVE VECTOR CONTROL MEASURES

Personal measures of protection can be adhered as follows:

- Use of insecticide-treated mosquito nets
- Personal protection measures
- Insecticide spraying
- The role of the health workers

4.8.1. Use of Insecticide-Treated Mosquito Nets

The promotion and use of insecticide-treated mosquito nets has become a leading strategy in malaria prevention and control. Surveys have shown dramatic reductions in the number of cases of malaria in communities using insecticidetreated mosquito nets. Regular use of treated nets has been shown to reduce child mortality by about 25%. Children sleeping under treated mosquito nets are less prone to anaemia, malnutrition and severe malaria.

In communities where a substantial proportion of people are using nets, fewer people are being bitten and this provides some community protection. In many countries mosquito nets and their re-treatment are still relatively costly. This is often due to high taxes and import duties levied on mosquito netting materials and insecticides by governments. To be most effective, mosquito nets must be re-
treated with recommended insecticides at least every 6 months to give maximum protection. They also protect against bites and stings of other insects. However, studies (see the case study entitled The Gambia: a question of price, on page 16 of this issue) have shown that if people have to pay for the net retreatment service, they are less likely to spend the necessary time and money having their nets dipped regularly in insecticides.

This issue of *The Prescriber* describes how to treat nets with insecticide, and describes an example of involving community funds in managing bednet sales and treatments.

Local communities can lobby their municipalities, governments, non-governmental organizations (NGOs), private companies etc. to mitigate the effects of public works projects, to fill up pits dug in the ground, to drain swamps, and to minimize deforestation and mining projects and/or movements of people which may trigger malaria epidemics. Health workers can encourage use of bednets and organize community action to fill in pools of water around the village, keep houses clean and put up curtains or screens on windows and doors.

4.8.2. Personal Protection Measures

Mosquito coils and body repellents (sprays and lotions) are often used for individual protection but they are not effective for general use as a control
measure and are relatively expensive. In particular, they may be useful to protect an individual from a non-endemic area or a primigravida. It is advisable for everyone to wear long protective clothing while outdoors to prevent mosquito bites, and to put wire screens on windows.

4.8.3. Insecticide Spraying

During the 1950s and 1960s, the principal strategy in controlling malaria was vector control. The vector of malaria is the Anopheles mosquito; the aim was to eradicate this mosquito, mainly through spraying with insecticides. Three problems arose: spraying was expensive; there were environmental problems with insecticides (especially DDT); and the mosquitoes became increasingly resistant to the insecticides. However, some vector control programmes were quite effective, especially in Latin America, and selective spraying continues to be used in certain circumstances. For example, it is still a recommended strategy for epidemic prevention and control amongst specifically targeted groups and areas, such as refugee populations or in urban settings. To be effective, vector control interventions must be targeted and have clear objectives, especially when used to prepare for an expected malaria epidemic.

Globally, DDT is targeted to be phased out and replaced by more environmentally friendly insecticides during the next 10 years. Many countries in Europe and North America have already banned the use of DDT.
4.8.4. The Role of the Health Worker

The two main ways to reduce the spread of malaria are the use of insecticide-treated mosquito nets, and early diagnosis and prompt treatment of malaria cases. The health worker plays an enormously important role in both these approaches. His or her ability to increase understanding about malaria and then promote the use of bednets can reduce the mortality rates of children within any community. The health worker also needs good knowledge of the diagnosis of malaria, and familiarity with the correct treatment recommended in each country, to reduce infections and save lives.

Having good knowledge of malaria is probably the single most important aspect of a health worker’s skills in preventing and controlling malaria. Sharing that knowledge with others is also important. Many people in malaria affected areas do not know enough about the disease to protect them from infection. UNICEF considers the training of health workers and support for community awareness and participation in malaria programmes as top priorities.

4.9. RESEARCH ON MALARIA

As the lessons of the past decades have convincingly demonstrated, conquering malaria is difficult. No one anticipates a quick victory even if new malaria drugs hit the market, or a vaccine proves highly successful. Rather,
researchers and health planners expect their best chances lie in a many-sided
attack, drawing upon a variety of weapons suited to local environments. Skillfully
combining several approaches, both old and new, may at last make it possible to
outmaneuver these persistent and deadly parasites.

4.9.1. Medicine

Medicines to treat malaria have been around for thousands of years. Perhaps the best known of the traditional remedies is quinine, which is derived
from the bark of the cinchona tree. The Spanish learned about quinine from
Peruvian Indians in the 1600s. Export of quinine to Europe, and later the United
States, was a lucrative business until World War II cut off access to the world
supply of cinchona bark. In the 1940s, an intensive research program to find
alternatives to quinine gave rise to the manufacture of chloroquine and numerous
other chemical compounds that became the forerunners of modern antimalarial
drugs.

4.9.2. Genetic mechanisms

Unfortunately, malaria parasites in many geographic regions have become
resistant to alternative drugs, many of which were discovered only in the last 30
years. Even quinine, the long-lived mainstay of malaria treatment, is losing its
effectiveness in certain areas.
To address the problem of drug-resistant malaria, scientists are conducting research on the genetic mechanisms that enable *Plasmodium* parasites to avoid the toxic effects of malaria drugs. Understanding how those mechanisms work should enable scientists to develop new medicines or alter existing ones to make drug resistance more difficult. By knowing how the parasite survives and interacts with the human host during each distinct phase of its development, researchers also hope to develop drugs that attack the parasite at different stages.

4.9.3. National Institute of Allergy and Infectious Diseases (NIAID)

NIAID scientists are also working to understand how *P. falciparum* has adapted to survive and grow within RBCs. An important category of these adaptations involves the trafficking of nutrients across various membranes of the infected RBC. To this end, researchers have identified two nutrient channels unique to the infected cell and plan to study these further to identify their genetic bases and to develop detailed mechanistic models of nutrient transport. With these models, they may be able to design channel blockers that interfere with the parasite’s ability to acquire needed nutrients. These blockers may prove to be novel and useful drugs for treating malaria.

Finally, NIAID scientists are unraveling the mechanisms of natural resistance to malaria infection, which is yielding valuable information for new antimalarial drug development. For example, in regions of West Africa, up to one-
fourth of children carry hemoglobin C, a variant of hemoglobin that can reduce the risk of severe and fatal malaria by as much as 80 percent. The way hemoglobin C protects people, however, had been puzzling.

4.9.4. Other Research Efforts

As with other diseases of worldwide importance, a critical aspect of our future ability to control malaria will depend on the skills and expertise of scientists, health care providers, and public health specialists working in malaria-endemic regions. Therefore, strengthening the research capabilities of scientists in these areas is another major focus of these efforts.

Through its support of the Malaria Research and Reference Reagent Resource Center (MR4), NIAID provides well-characterized research materials to scientists in malaria-endemic areas. NIAID also works closely with national and international organizations involved in malaria research and control. In addition, NIAID was a founding member of the Multilateral Initiative on Malaria, which emphasizes strengthening research capacity in Africa.

4.10. CONCLUSION

Although malaria has been virtually eradicated in the United States and other regions with temperate climates, it continues to affect hundreds of people in this country every year. The Centers for Disease Control and Prevention (CDC)
estimates 1,200 cases of malaria are diagnosed each year in the United States. People who live in the United States typically get malaria during trips to malaria-endemic areas of the world.

The pace of the battle accelerated rapidly when the insecticide DDT and the drug chloroquine were introduced during World War II. DDT was remarkably effective and could be sprayed on the walls of houses where adult Anopheles mosquitoes rested after feeding. Chloroquine has been a highly effective medicine for preventing and treating malaria.

At the same time, scientists are intensively researching ways to develop better eapons against malaria, including

- Sophisticated techniques for tracking disease transmission worldwide
- More effective ways of treating malaria
- New ways, some quite ingenious, to control transmission of malaria by mosquitoes
- A vaccine for blocking malaria’s development and spread

People have worked for centuries to control malaria and were successful in eradicating it from most of North America early in the 20th century. Certain human activities, however, have inadvertently worsened the spread of malaria.
City conditions, for example, can create new places for mosquito larvae to develop. Agricultural practices also can affect mosquito breeding areas. Although the draining and drying of swamps gets rid of larval breeding sites, water-filled irrigation ditches may give mosquitoes another area to breed. In addition, because farmers use the same pesticides on their crops as those used against malaria vector mosquitoes, the problem of insecticide-resistant mosquitoes is growing. Modern transportation also contributes to the spread of the disease, moving travelers and occasionally mosquitoes between malaria-endemic and non-endemic regions.
REFERENCES


