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Review Article



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Review on Pathology and Chemoprophylaxis of Malaria

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Abstract

Malaria, transmitted by female *Anopheles* mosquitoes biting during night time, from sunset to dawn, is the most important parasitic disease worldwide. Five species (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and, as recently discovered, *Plasmodium knowlesi*) can cause disease in humans. At first, malaria symptoms may be unspecific, including joint pain, asthenia and abdominal pain; followed by high fever, shivering, and anorexia and vomiting. The most severe form is caused by *Plasmodium falciparum*. The importance of behavioral preventive measures (bed nets, repellents, etc.), adequate chemoprophylaxis and increase the awareness of Pathophysiology, health measures of disease to be taken. Coming to the mainstay of malaria diagnosis has been the microscopic examination of blood, utilizing blood films for confirmation of malaria and further follow up sanitation and chemoprophylaxis of the disease.

Key words: Malaria, *Anopheles* mosquitoes, chemoprophylaxis

Introduction

Malaria is a parasitic disease transmitted by parasites that cause malaria *Plasmodiumovale*, *P. malariae*, *P. knowlesi*, *P. vivax*, and *P. falciparum*. The last 2 are the most common, primarily, malaria is an infection of the red blood cells, causing recurring fever of sudden on set. Malaria caused by *P. falciparum* is lifethreatening and can cause multiple organ damage, coma and death. Malaria is spread by female *Anopheles* mosquitoes. The parasite enters the body in mosquito saliva when a person is bitten by an infected mosquito. The parasite first infects the liver where it begins to multiply. After some days, the resulting parasites are released into the blood stream to infect the red blood cells, where they continue to multiply, eventually bursting the red blood cells and further infecting others. If they reach high numbers they may cause severe disease or even death. Some of the parasites in the red blood cells develop into the sexual stages (gametocytes). If these stages are ingested when a mosquito bites an infected person,

they develop in the gut of the mosquito for 10 –14 days, and then enter the salivary glands, ready for the next bite. Malaria is found throughout the tropical and subtropical regions of the world. Areas of high transmission are found predominantly in rural areas in South America (e.g. Brazil), south east Asia (e.g. Thailand, Indonesia and East Timor), Western Pacific (Papua New Guinea, Solomon Islands and Vanuatu) and throughout sub-Saharan Africa [1, 2].

The last case of locally acquired malaria in the Northern Territory was in 1962 and Australia was declared free of malaria by the World Health Organisation (WHO) in 1981. However, a number of species of *Anopheles* mosquito exist in the NT and the malaria parasite could be re-introduced into local mosquitoes if infected travellers from overseas are bitten here. The outcome of a malaria infection is a consequence of interactions between host, parasite and environmental factors. As such attempts to correlate out come with a single immunological parameter often results spurious associations that do not hold in different circumstances. This situation is exacerbated by the lack of natural animal models for human malaria from which observations could reliably be extrapolated consequently; much of our understanding of malaria immunity is based on extrapolation of in vitro observations or deduced from phenomenological observations [2]. As is the case with immunity to other infections, immunity to malaria is the result of a combination of genetic resistance, non-adaptive immunity, and acquired or adaptive immunity. This chapter will mainly focus on immunity to *Plasmodium falciparum* malaria because it accounts for largest proportion of disease and practically all malaria mortality.

Definition of Malaria:

An infectious disease caused by protozoan parasites from the plasmodium family that can be transmitted by the sting of the Anopheles mosquito or by a contaminated needle or transfusion. Falciparum malaria is the most deadly type. Malaria is a blood disease caused by a parasite that is transmitted from human-to-human by the *Anopheles* mosquito. Malaria is a preventable and treatable disease [2]. The word malaria comes from 18th century Italian *mala* meaning "bad" and *aria* meaning "air". Most likely, the term was first used by Dr. Francisco Torti, Italy, when people thought the disease was caused by foul air in marshy areas.

History of malaria

The history of malaria predates humanity, as this ancient disease evolved before humans did. Malaria, a widespread and potentially lethal infectious disease, has afflicted people for much of human history, and has affected settlement patterns. The prevention and treatment of the disease have been investigated in science and medicine for hundreds of years, and, since the discovery of the parasite which causes it, attention has focused on its biology. These studies have continued up to the present day, since no effective Malaria vaccine has yet been developed and many of the older anti malarial drugs are losing effectiveness as the parasite evolves high levels of drug resistance. As malaria remains a major public health problem, causing 250 million cases of fever and approximately one million deaths annually, understanding its history is key [3]. Human malaria likely originated in Africa and has coevolved along with its hosts, mosquitoes and non-human primates. The first evidence of malaria parasites was found in mosquitoes preserved in amber from the Paleocene period that are approximately 30 million years old. Malaria may have been a human pathogen for the entire history of the species. 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).^[7] 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 [3].

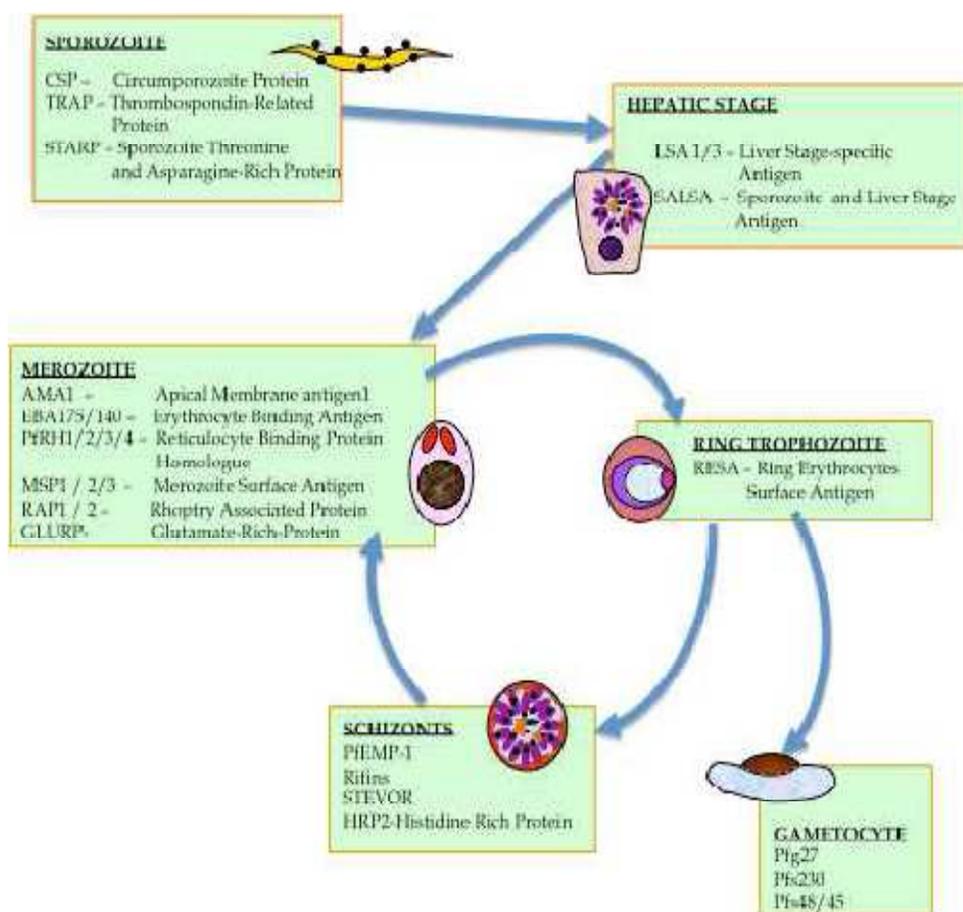
Left: regions in Africa where *Plasmodium falciparum* malaria was transmitted before control was introduced. Right: frequencies of sickle-cell heterozygotes in the indigenous African population. References to the unique periodic fevers of malaria are found throughout recorded history. According to legend, the Chinese emperor Huang Di (Yellow Emperor, 2697–2590 BCE) ordered the compilation of a canon of internal medicine. The Chinese Huangdi Neijing (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. The presence of malaria in Egypt from circa 800 BC onwards has been confirmed using DNA based methodologies. 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 idea that the disease came from the foul gasses released from soil, water and air persisted throughout the nineteenth century [4].

Malaria was once common in most of Europe and North America, where it is now for all purposes non-existent. The coastal plains of southern Italy, for example, fell from international prominence (the Crusaders going by sea to the Holy Land took ship at Bari) when malaria expanded its reach in the sixteenth century. At roughly the same time, in the coastal marshes of England, mortality from "marsh fever" or "tertian ague" ("the ague" from Latin "*febris acuta*") was comparable to that in sub-Saharan Africa today. William Shakespeare was born at the start of the especially cold period that climatologists call the "Little Ice Age", yet he was aware enough of the ravages of the disease to mention it in eight of his plays. Throughout history the most critical factors in the spread or eradication of disease have been human behavior (shifting population centers, changing farming methods and the like) and living standards. Precise statistics do not exist because many cases occur in rural areas where people do not have access to hospitals or the means to afford health care. As a consequence, the majority of cases are undocumented. Poverty has been and remains a reason for the disease to remain while it has undergone a decline in other locations. Climate change is likely to affect future trends in malaria transmission, but the severity and geographic distribution of such effects is currently uncertain, though attracting increasing scientific attention [5].

Life Cycle of Malaria:

Plasmodium parasites primary host and transmission vectors are female anopheles mosquitoes. Humans and other vertebrates are secondary hosts. The mosquitoes first take in the parasite by feeding on the blood of an infected person [6].

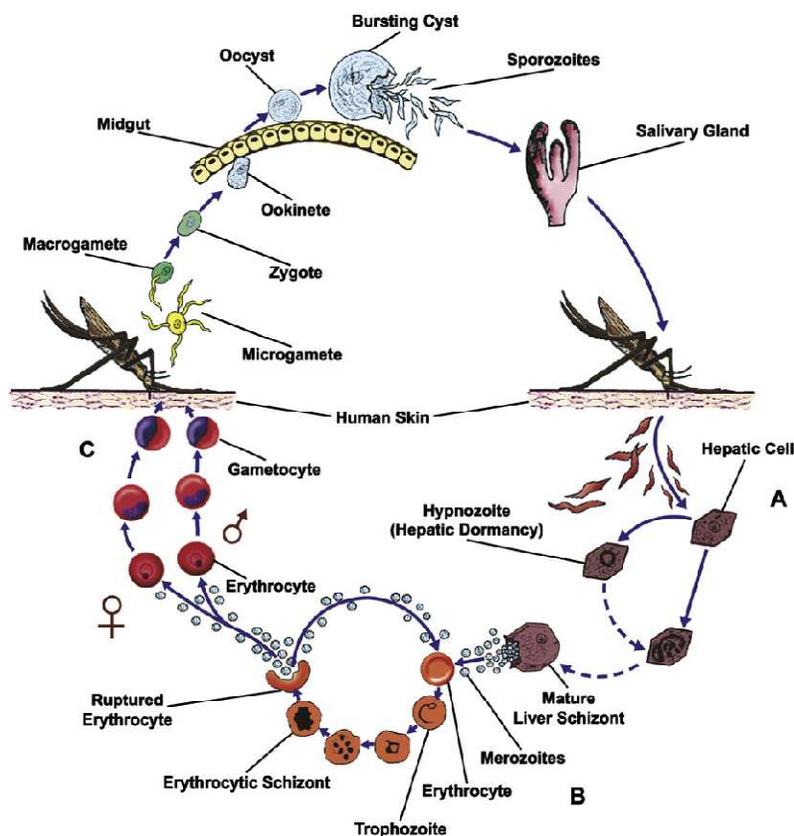


Control efforts:

Entomologist Raymond Corbett Shannon discovered disease-bearing *Anopheles gambiae* mosquitoes living in Brazil, likely brought there by plane or fast mail steamer^[21]. This species of mosquito is a particularly efficient vector for malaria and is native to Africa.^[22] In 1938, the introduction of this new mosquito vector caused the greatest epidemic of malaria ever seen in the new world. However, complete eradication of *A.gambiae* from north-east Brazil and thus from the New World was achieved in 1940 by meticulous application of Paris green to breeding places and of pyrethrum spray-killing to adult resting places [7]. Starting in World War II, DDT was used as insecticide to combat insect vectors carrying malaria, which was endemic in most tropical regions of the world. The first goal was to protect soldiers, but it was widely adopted as a public health device. In Liberia, for example, the United States had large military operations during the war and the U.S. Public Health Service began the use of DDT for indoor residual spraying (IRS) and as a larvicide, with the goal of controlling malaria in Monrovia, the Liberian capital. In the early 1950s, the project was expanded to nearby villages. In 1953, the World Health Organization (WHO) launched an antimalaria program in parts of Liberia as a pilot project to determine the feasibility of malaria eradication in tropical Africa. However these projects encountered a spate of difficulties that foreshadowed the general retreat from malaria eradication efforts across tropical Africa by the mid-1960s [8].

Netic resistance to malaria:

Genetic resistance to malaria occurs through both modifications of the immune system that enhance immunity to this infection and also by changes in human red blood cells that hinder the malaria parasite's ability to invade and replicate within these cells. Host resistance to malaria therefore involves not only blood cell genes such as abnormal haemoglobins, Glucose-6-phosphate dehydrogenase deficiency, and Duffy antigens, which provide innate resistance, but also genes involved in immunity such as the major histocompatibility complex genes, which regulate adaptive immune responses.^[25] The resistance provided by modified blood cells aids survival through the dangerous years of early childhood, while the potent protection mediated by adaptive immune responses is more important in older children and adults living where malaria is endemic [9]. Malaria has placed the strongest known selective pressure on the human genome since the origination of agriculture within the past 10,000 years.^{[26][27]} Several inherited variants in erythrocytes have become common in formerly malarious parts of the world as a result of selection exerted by this parasite [11].



Pathology of Malaria within Human Hosts

Once within the humans the malaria parasite undergoes two phases an exoerythrocytic and an erythrocyte phase.

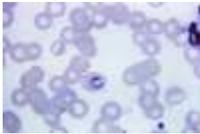
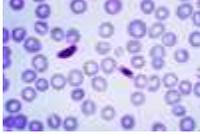
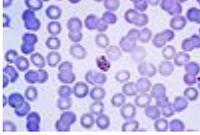
Exoerythrocyte Phase

The exoerythrocytic phase involves maturation and development of parasite in the liver. When an infected mosquito transmits the infection or sporozoites as it takes in a blood meal the sporozoites in mosquito's saliva enter the blood stream and migrate to the liver. The process of migration takes around 30 minutes after a bite. The sporozoites infect hepatocytes. This is followed by multiplication of sporozoites. This is known as asexual reproduction or multiplication. It takes around 6-15 days for this multiplication. The parasite then forms thousands of merozoites within the hepatocytes. The numerous merozoites lead to rupture of their host cells and escape into the blood. Sometimes the sporozoites may not immediately go into the exoerythrocytic phase merozoites, but instead productive hypnozoites that lie dormant in the liver. This is seen with *plasmodium vivax* and *plasmodium ovale*. The periods of dormancy may range over several months (typically 6-12 months to around 3 years). Hypnozoites are responsible for long incubation and late relapses in these two species of malaria [12]. The involvement of red blood cells is called the erythrocytic phase. In the RBCs the merozoites multiply further asexually and burst the RBCs as they multiply releasing the merozoites in blood. Each burst is associated with about of fever. The new merozoites then invade fresh red blood cells leading to further amplification. Several such amplification cycles occur. Each such amplification is thus characterized by a wave of fever. Some of merozoites develop into male and female gametocytes that may be further transmitted to mosquitoes. This completes the life cycle [13].

Diagnosis of Malaria:

The mainstay of malaria diagnosis has been the microscopic examination of blood, utilizing blood films. Although blood is the sample most frequently used to make a diagnosis, both saliva and urine have been investigated as alternative, less invasive specimens [14]. More recently, modern techniques utilizing antigen tests or polymerase chain reaction have been discovered, though these are not widely implemented in malaria endemic regions⁽³¹⁾⁽³²⁾. Areas that cannot afford laboratory diagnostic tests often use only a history of subjective fever as the indication to treat for malaria

Blood films:

Species	Appearance	Periodicity	Liver persistent
<i>Plasmodium vivax</i>		Tertian	Yes
<i>Plasmodium ovale</i>		Tertian	Yes
<i>Plasmodium falciparum</i>		Tertian	No
<i>Plasmodium malariae</i>		Quartan	No

The most economic, preferred, and reliable diagnosis of malaria is microscopic examination of blood films because each of the four major parasite species has distinguishing characteristics. Two sorts of blood film are traditionally used. Thin films are similar to usual blood films and allow species identification because the parasite's appearance is best preserved in this preparation. Thick films allow the microscopist to screen a larger volume of blood and are about eleven times more sensitive than the thin film, so picking up low levels of infection is easier on the thick film, but the appearance of the parasite is much more distorted and therefore distinguishing between the different species

can be much more difficult. With the pros and cons of both thick and thin smears taken into consideration, it is imperative to utilize both smears while attempting to make a definitive diagnosis [15]

Antigen Test

For areas where microscopy is not available, or where laboratory staff are not experienced at malaria diagnosis, there are commercial antigen detection tests that require only a drop of blood^[34]. Immunochromatographic tests (also called: malaria rapid diagnostic tests, Antigen-Capture Assay or "Dipsticks") have been developed, distributed and field tested. These tests use finger-stick or venous blood, the completed test takes a total of 15–20 minutes, and the results are read visually as the presence or absence of colored stripes on the dipstick, so they are suitable for use in the field. The threshold of detection by these rapid diagnostic tests is in the range of 100 parasites/ μ l of blood (commercial kits can range from about 0.002% to 0.1% parasitemia) compared to 5 by thick film microscopy [16].

Molecular Methods

Molecular methods are available in some clinical laboratories and rapid real-time assays (for example, QA-NASBA based on the polymerase chain reaction) are being developed with the hope of being able to deploy them in endemic areas. PCR (and other molecular methods) is more accurate than microscopy. However, it is expensive, and requires a specialized laboratory. Moreover, levels of parasitemia are not necessarily correlative with the progression of disease, particularly when the parasite is able to adhere to blood vessel walls. PCR (and other molecular methods) is more accurate than microscopy. However, it is expensive, and requires a specialized laboratory. Moreover, levels of parasitemia are not necessarily correlative with the progression of disease, particularly when the parasite is able to adhere to blood vessel walls. Therefore more sensitive, low-tech diagnosis tools need to be developed in order to detect low levels of parasitemia in the field [17].

Cause of Malaria

Malaria is caused by a single-celled parasite from the genus *Plasmodium*. More than 100 different species of *Plasmodium* exist. They produce malaria in many types of animals and birds, as well as in humans. Four species of *Plasmodium* commonly infect humans. *Plasmodium falciparum* is responsible for most malaria deaths, especially in Africa. The infection can develop suddenly and produce several life-threatening complications. *Plasmodium malariae* infections not only produce typical malaria symptoms but also can persist in the blood for very long periods, possibly decades, without ever producing symptoms. *Plasmodium ovale* is rare, can cause relapses, and generally occurs in West Africa. *Plasmodium vivax*, the most geographically widespread of the species, produces less severe symptoms [18].

Signs and Symptoms:

The typical fever patterns of the different types of malaria

The signs and symptoms of malaria typically begin 8–25 days following infection^[36]; however, symptoms may occur later in those who have taken antimalarial medications as prevention.^[37] Initial manifestations of the disease—common to all malaria species—are similar to flu-like symptoms,^[38] and can resemble other conditions such as septicaemia, gastroenteritis, and viral diseases.^[37] The presentation may include headache, fever, shivering, joint pain, vomiting, haemolytic anemia, jaundice, haemoglobin in the urine, retinal damage [19] and convulsions. The classic symptom of malaria is paroxysm—a cyclical occurrence of sudden coldness followed by rigor and then fever and sweating, occurring every two days (tertian fever) in *P. vivax* and *P. ovale* infections, and every three days (quartan fever) for *P. malariae*. *P. falciparum* infection can cause recurrent fever every 36–48 hours or a less pronounced and almost continuous fever [20]. Severe malaria is usually caused by *P. falciparum* (often referred to as falciparum malaria). Symptoms of falciparum malaria arise 9–30 days after infection.^[38] Individuals with cerebral malaria frequently exhibit neurological symptoms, including abnormal posturing, nystagmus, conjugate gaze palsy (failure of the eyes to turn together in the same direction), opisthotonus, seizures, or coma [21].

Treatment of malaria:

According to the CDC (centers for disease control and prevention), the following drugs are commonly used for treating malaria: Artemisia derivatives (not licensed in the USA, common elsewhere), atovaquone-proguanil (Malarone), chloroquine doxycycline, mefloquine (Lariam), quinine, sulfadoxine-pyrimethamine (Fansidar) Also, primaquine is effective against hypnozoites (the dormant parasite liver forms) and prevents recurrences (relapses). Primaquine should not be given to expectant mothers, or patients who are deficient in glucose-6-phosphate dehydrogenase G6PD. A screening test excludes G6PD deficiency [22].

Conclusion

These results point to several notable conclusions. First, it is entirely possible for an economy to arrive at a “malaria trap,” in which sickness begets poverty and poverty makes disease prevention unaffordable. In the model economy, we can quantify the magnitude of this “malaria trap.” It can reduce income per capita by about half. By point of comparison, Gallup and Sachs (2000) note that the 44 countries with intensive malaria burdens in 1995 had per capita income of \$1,526, compared with \$8,268 for the 106 countries without intensive malaria burden. Our model suggests that the disease alone could account for just under half of this income gap. Some studies have shown that malaria-mediated evolutionary selection has involved 2 main aspects: strong selective pressure (e.g. in the case of the higher frequency HbS allele found in malaria exposed populations) and independent evolutionary responses developed by different populations both at a global and local level. The best example at a global level could be given by the HBB gene in which 3 different SNPs (HbS, HbC and HbE) have been shown to confer protection against malaria because the mutations produced affect hemoglobin functionality. The burden of disease is intolerable yet tools are available to make an enormous impact on death and suffering. Investment in control and elimination will have enormous returns for personal health and cumulative benefits for a safer and healthier future for the whole world. It is up to the leaders of this generation to ensure that future generations will benefit from a massive investment in the next decade.

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