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Literature Review

WHAT IS MALARIA?

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ABSTRACT

Malaria persists as an undiminished global problem and still is the cause of much human morbidity and mortality. Although the disease has been eradicated in many temperate zones, it continues to be endemic throughout much of the tropics and subtropics. Many tools for understanding its biology and epidemiology are well developed, with a particular richness of comparative genome sequences. Studies of the epidemiology, prevention, and treatment of human malaria have already been influenced by the availability of molecular methods, and analyses of parasite polymorphisms have long had useful and highly informative applications. The molecular epidemiology of malaria is currently undergoing its most substantial revolution as a result of the genomic information and technologies that are available in well-resourced centers. However, great progress in malaria control has been made in some highly endemic countries. Vector control is assuming a new importance with the significant reductions in malaria burden achieved using combined malaria control interventions. Education of health workers and communities about malaria prevention, diagnosis and treatment is a vital component of effective case management, especially as diagnostic policies change.

Key words: *malaria, Plasmodium, Anopheles Mosquito, parasite detection, malaria control*

INTRODUCTION

Malaria is probably one of the oldest diseases known to mankind that has had profound impact on our history. For centuries it prevented any economic development in vast regions of the earth. It continues to be a huge social, economical and health problem, particularly in the tropical countries. Malaria has been and still is the cause of much human morbidity and mortality. Although the disease has been eradicated in many temperate zones, it continues to be endemic throughout much of the tropics and subtropics. Forty percent of the world's population lives in endemic areas. Epidemics have devastated large populations a malaria poses a serious barrier to economic progress in many developing countries.

Malaria is caused by members of the genus *Plasmodium*. *Plasmodium* species are apicomplexa and exhibit a heteroxenous life cycle involving a vertebrate host and an arthropod vector. Vertebrate hosts include: reptiles, birds, rodents, monkeys and humans. *Plasmodium* species are generally host and vector specific in that each species will only infect a limited range of hosts and vectors. Four distinct species infected humans: *P. falciparum*, *P. vivax*, *P. ovale* and *P malariae.* The four human parasite species differ in regards to their morphology, details of their life cycles, and their clinical manifestations. *Plasmodium falciparum* is the most common species in tropical areas and is transmitted primarily during the rainy season. This species is the most dangerous, accounting for half of all clinical cases of malaria and 90 percent of deaths from the disease. *Plasmodium vivax* is the most widely distributed parasite, existing in temperate as well as tropical climates. *Plasmodium malariae* can also be found in temperate and tropical climates but is less common than *Plasmodium vivax*. *Plasmodium ovale* is a relatively rare parasite, restricted to tropical climates and found primarily in eastern Africa.[4,8] Based on field survey on malaria at Flores island, East Nusa Tenggara Province, Indonesia, Tantular *et al* found single infections with either *Plasmodium falciparum* or *P. vivax* were predominantly , mixed infection with *P. vivax* and *P. malariae* and 6 triple infections with *P. falciparum, P. vivax, P. malariae*.[20]

Plasmodium parasites undergo many stages of development, and their complete life cycle occurs in both humans and mosquitoes. The parasites are transmitted to humans by female mosquitoes of the genus *Anopheles*. About 60 of the 390 species of *Anopheles* mosquito transmit the malaria parasite. Of these, only a dozen

species are important in the transmission of malaria worldwide. Usually just one or two species play a role in malaria transmission in a particular region where the disease is prevalent. It is a disease that can be treated in just 48 hours, yet it can cause fatal complications if the diagnosis and treatment are delayed. It is re-emerging as the first Infectious Killer and it is the Number one Priority Tropical Disease of the World Health Organization. Malaria ranks third among the major infectious diseases in causing deaths after pneumococcal acute respiratory infections and tuberculosis. It is expected that by the turn of the century malaria would be the number one infectious killer disease in the world. (Trigg and Kondrachine, 1998; Rosemary, 2010).

HISTORY OF PLASMODIUM PARASITES

Malaria is an ancient disease that has plagued humans throughout history. The Greek physician Hippocrates described malaria in his writings during the 400s BC. Throughout history and even today outbreaks of malaria have often been associated with warfare, migrations, and other societal disruptions. More soldiers have been lost to malaria than to bullets in the wars of the 20th century.

Historians believe that malaria was brought to the Western Hemisphere by European explorers. However, the exact cause of malaria was not understood until the closing years of the 19th century. In 2002 an international team of scientists deciphered the genome (genetic makeup) of *Plasmodium falciparum* and other malaria parasites. Scientists hope to use information gained from researching the parasite's genome to design more effective antimalaria drugs and vaccines. Scientists have also decoded the genome sequence of *Anopheles gambiae*, one of the most common malaria mosquitoes. Insecticides that target specific proteins produced by one or more genes in this mosquito's genome may one day be used to control and possibly eliminate the mosquito from many areas.[1,3]

The tropical disease malaria, which results in more than one million deaths annually, is considered one of the most significant infectious diseases worldwide. Malaria is caused by protozoan parasites of the genus Plasmodium and transmitted by blood-feeding Anopheline mosquitoes. Malaria infects hundreds of millions of people worldwide and kills an estimated 900,000 a year, taking an especially high toll on children in sub-Saharan Africa. At present, at least 300,000,000 people are affected by malaria globally, and there are between 1,000,000 and 1,500,000 malaria deaths per year. Malaria parasites have been with us since the dawn of time. They probably originated in Africa (along with mankind) and fossils of mosquitoes up to 30 million years old show that the vector for malaria was present well before the earliest history.[22]

The Plasmodium parasites are highly specific, with man as the only vertebrate host and Anopheles mosquitoes as the vectors. This specificity of the parasites also points towards a long and adaptive relationship with our species. Malaria is generally endemic in the tropics, with extensions into the subtropics. Malaria in travellers arriving by air is now an important cause of death in non-malarious areas, and this is not helped by the common ignorance or indifference of travellers to prophylaxis. Distribution varies greatly from country to country, and within the counties themselves, as the flight range of the vector from a suitable habitat is fortunately limited to a maximum of 2 miles, not taking account of prevailing wind etc.[4,5]

In 1990, 80% of cases were in Africa, with the remainder clustered in nine countries: India, Brazil, Afghanistan, Sri-Lanka, Thailand, Indonesia, Vietnam, Cambodia and China. Current data for Africa is unavailable. The disease is endemic in 91 countries currently, with small pockets of transmission in a further eight. *Plasmodium falciparum* is the predominant species, with 120,000,000 new cases and up to 1,000,000 deaths per year globally. It is the *Plasmodium falciparum* species which has given rise to the formidable drug resistant strains emerging in Asia. In 1989, WHO declared malaria control to be a global priority due to the worsening situation, and in 1993, the World Health Assembly urged member states and WHO to increase control efforts.[5,22]

EPIDEMIOLOGY

Malaria is primarily a disease of the tropics and subtropics and is widespread in hot humid regions of Africa, Asia and South and Central America. Currently malaria is endemic in more than 100 countries and 40% of the world's population lives in areas at risk for infection. The level of malaria transmission varies in different regions, countries and also within countries. Endemic regions are characterized by warm temperatures and rainfall, both suitable for mosquito breeding, and where populations of human hosts and malaria parasites co-exist. Because of the climatic conditions required, seasonal maps can be drawn up that allow prediction of when transmission will be at its highest and where epidemics are likely to occur. Such seasonal information should help with the development of malaria control calendars and assist health services in appropriately focusing their control activities, such as drug procurement and anti-vector measures. The map shows areas of the world with different levels of endemicity or transmission intensity.[4,22]

Malaria is prevalent in sub-Saharan Africa, as well as other tropical and sub-tropical regions such as Central and South America, Asia, and the Middle East. The geographic distribution of malaria is coordinate with the mosquito vector. As a result, malaria is generally not found in high altitude places. Though *Anopheles* mosquitoes can be found in the United States, public health interventions have disrupted parasite transmission. Most cases of malaria in the United States are therefore "imported malaria," or malaria

acquired by a person traveling from an endemic region to the United States.[21]

Factors which may precipitate a malaria epidemic fall into two categories: natural (climatic variations, natural disasters), and man-made (conflict and war, agricultural projects, dams, mining, logging). Most of these factors modify the physical environment, and increase the capacity of mosquitoes to transmit malaria. Some factors also result in massive population movements that expose non-immune populations to malaria infection The epidemiology of malaria is very important in understanding which populations will be most at risk, so that control programmes can be designed accordingly.[19,22]

BIOLOGY OF PLASMODIUM PARASITES AND ANOPHELES MOSQUITOS

Malaria, a parasitic infection caused by Plasmodium spp., requires two hosts: a human and a mosquito. Mosquito bites transmit malaria to people. Before mosquitoes were identified as the vectors of malaria, people thought the disease was the result of drinking bad water or breathing bad air (in fact, *malaria* means bad air). Even after scientists realized mosquitoes carried malaria, many believed infection resulted from drinking water in which mosquitoes had died. Today, scientists know that *Plasmodium* spp., the parasites that cause malaria, require both the mosquito and the vertebrate host to complete their life cycle. When someone has symptoms of malaria, the parasites circulate in the blood stream; at this stage in their life cycle they are found inside red blood cells (erythrocytes). The so-called erythrocytic phase of the malaria parasite culminates with the development of gametocytes - male and female malarial parasites. When a mosquito bites a person who has malaria, it sucks both blood and malarial parasites into its stomach. Most of these parasites die and are digested with the blood, but if the mosquito is an *Anopheles* sp. mosquito, and there are gametocytes in the ingested blood, the gametocytes develop to gametes. Once an *Anopheles* mosquito is infected with malaria, it remains infected for life and can infect a human each time it takes a blood meal. It appears that infected *Anopheles* mosquitoes feed more often than those that are not infected, increasing the potential for the parasite to be passed on.[16]

The Plasmodium genus of protozoal parasites (mainly *P.falciparum, P.vivax, P.ovale*, and *P.malariae*) have a life cycle which is split between a vertebrate host and an insect vector. The Plasmodium species, with the exception of *P.malariae* (which may affect the higher primates) are exclusively parasites of man. The mosquito is always the vector, and is always an Anopheline mosquito, although, out of the 380 species of Anopheline mosquito, only 60 can transmit malaria. Only female mosquitos are involved as the males do not feed on blood.[14,16]

TRANSMISSION OF MALARIA

Infectious Bites

Each year more than 200 million people develop malaria. More than one million people die from malaria each year. When a mosquito bites, it injects a small amount of fluid. If the mosquito has *Plasmodium* sp. sporozoites in its salivary glands, some of the sporozoites enter the prey bloodstream. Sporozoites remain in the blood only minutes to hours before they invade liver cells, where they begin multiplying again.

In Cameroon, the researchers recorded how often people were bitten by a mosquito that carried malaria parasites. They also examined the number of transmittable parasites in the blood of infected persons. The number of gametocytes per person was season and age dependent. Children were found to be by far the most important source of malaria transmission in the area. People who live in areas where malaria is prevalent, can develop a natural immunity that stops the development of the parasite in the mosquito. This prevents the parasite from spreading further. The presence of this immunity, the so-called transmission-reducing activity, is determined using a laboratory test. Van der Kolk discovered that people who are often infected with malaria could quickly acquire this immunity. He also found that people with higher numbers of gametocytes are more frequently immune.[10,16]

Malaria parasites are transmitted from the vertebrate host to the mosquito vector by sexual blood stages (gametocytes). When taken up in the bloodmeal by the engorging female mosquito, male gametocytes (microgametocytes) undergo exflagellation, producing up to eight male gametes; a female gametocyte (macrogametocyte) produces only one female gamete, which is fertilized by a single male gamete. The gametocyte sex ratio tends to be female-biased in all species of malaria parasites and several authors have considered that the theory of local mate competition, which successfully explains many other cases of biased sex ratios · determines the gametocyte sex ratio of malaria parasites. According to this theory, when an infection consists of a few parasite clones, whose offspring will mate among themselves, a female-biased sex ratio is favored by natural selection, because it will reduce competition among brothers for mates. However, empirical data are conflicting and the mechanism of gametocyte sex determination in malaria parasites remains unknown. Gametocyte sex is not determined by segregation of sex-determining genes or chromosomes, because malaria parasites are haploid in the vertebrate host and a single clone can produce both male and female gametocytes.[2,13]

Other Modes of Transmission

Rarely malaria can spread by the inoculation of blood from an infected person to a healthy person. In this type of malaria, asexual forms are directly inoculated into the

blood and pre-erythrocytic development of the parasite in the liver does not occur. Therefore, this type of malaria has a shorter incubation period and relapses do not occur.

1. Blood transfusion (Transfusion malaria)
   This is fairly common in endemic areas. Following an attack of malaria, the donor may remain infective for years (1-3 years in *P. falciparum*, 3-4 years in *P. vivax*, and 15-50 years in *P. malariae*. Most infections occur in cases of transfusion of blood stored for less than 5 days and it is rare in transfusions of blood stored for more than 2 weeks. The clinical features of transfusion malaria occur earlier and any patient who has received a transfusion three months prior to the febrile illness should be suspected to have malaria. Donor blood can be tested with indirect fluorescent antibody test or ELISA, and direct examination of the blood for the parasite may not be helpful. In transfusion malaria, pre-erythrocytic schizogony does not occur and hence relapses due to dormant hepatic forms also does not occur.
2. Mother to the growing fetus (Congenital malaria)
   Intrauterine transmission of infection from mother to child is well documented. Placenta becomes heavily infested with the parasites. Congenital malaria is more common in first pregnancy, among non - immune populations.
3. Needle stick injury
   Accidental transmission can occur among drug addicts who share syringes and needles. Therapeutic inoculation of malarial parasites, so as to induce fever, was a mode of treatment for neurosyphilis.[1,12]

DETECTION OF MALARIA PARASITES

Microscopic examination is the primary method of malaria parasite detection and species identification, although problems with this have been recognized for some time have not diminished in recent years. Even the most skillful morphological analysis of stained parasites on blood films is not a very reliable basis for determining the identity of a malaria parasite species. Difficulties are compounded when infections contain more than one parasite species or when an unusual species is present. Although the peripheral blood smear examination that provides the most comprehensive information on a single test format has been the "gold standard" for the diagnosis of malaria, the immunochromatographic tests for the detection of malaria antigens, developed in the past decade, have opened a new and exciting avenue in malaria diagnosis.[13]

Identification of malaria parasites in peripheral blood samples can now be most reliably performed by analysis of DNA, and this, to some extent, transforms the possibilities for diagnosis and epidemiology of malaria. Parasite morphology has proved unsuitable for a systematic analysis of the relationships among the different species. Other parasitological features, such as data on the course of experimental infections (including periodicity of replication in the blood), also have little reliability for systematic purposes. The use of PCR-based methods to detect malaria parasites in blood samples increases the sensitivity of detection compared with microscopy. Qualitative PCR protocols that are robust, sensitive, and species specific have been available since the 1990s, and there are now several quantitative PCR methods that allow estimation of parasitemia levels as well as positivity.[15,17]

Thick-film microscopy can allow the examination of ~0.1 to 1 μl of blood (50 to 500 high-power fields with ~0.002 μl per field) and, thus, the detection of more than ~10 parasites μl^{-1}. Most applications of PCR typically involve amplification of DNA template from the equivalent of 1 to 10 μl blood and are thus either slightly more or up to 100 times more sensitive than microscopy. DNA template can be prepared from larger volumes of blood to give even higher sensitivity, with detection of ~20 parasites ml^{-1} being achieved, which is useful in clinical vaccine trials in which the time to first detectable blood-stage parasitemia is the endpoint (Singh *et al*., 1999; Mangold *et al*., 2005).

Sensitive PCR methods for parasite detection have been used to good effect in epidemiological studies, revealing surprisingly high proportions of individuals that have persistent asymptomatic infections in some populations in areas of endemicity. Use of real-time quantitative PCR methods is being evaluated in clinical diagnostic laboratories in countries of endemicity with good resources and reference laboratories in countries with substantial numbers of imported malaria cases. However, there is a limitation to the information provided by any method that samples peripheral blood for estimation of *P. falciparum* parasitemia, as sequestered mature asexual parasites may sometimes outnumber those in the peripheral blood (Roper *et al*., 1996; Singh *et al*., 1999).

Signs and Symptoms

Malaria is a febrile illness characterised by fever and related symptoms. However it is very important to remember that malaria is not a simple disease of fever, chills and rigors. In fact, in a malarious area, it can present with such varied and dramatic manifestations that malaria may have to be considered as a differential diagnosis for almost all the clinical problems. Malaria is a great imitator and trickster, particularly in areas where it is endemic.[18]

All the clinical features of malaria are caused by the erythrocytic schizogony in the blood. The growing parasite progressively consumes and degrades intracellular proteins, principally hemoglobin, resulting in formation of the 'malarial pigment' and hemolysis of the infected red cell. This also alters the transport properties of the red cell membrane, and the red cell becomes more spherical and less deformable. The rupture of red blood cells by merozoites releases certain factors and toxins.[8,21]

Clinical manifestations of malaria are attributable to the blood stage component of the parasite life cycle. Symptoms and symptoms of malaria include non-specific

flu-like symptoms, malaise, abdominal pain, anemia, splenomegaly, chills, and fever. The fevers of malaria have a periodic onset that is commisserate with asexual parasite development. This periodic fever, however, is frequently not seen clinically, and therefore is not often helpful in distinguishing malaria from other causes of fever. For example, fevers arising from infection with *P. falciparum* emerge every 48 hours. This corresponds to the time needed for *P. falciparum* to proceed from the ring stage to rbc rupture and invasion of other rbcs, a point at which the parasite once again adopts the morphologically-ascribed ring form. Anemia results from the rupture of infected erythrocytes, splenomagaly, and vascular sequestration. More severe manifestations of malaria include cerebral malaria, severe anemia, renal failure, respiratory distress, and death. The death rate from Falciparum malaria may be as high as 40% in non-immune individuals.[6,12]

IN AN ENDEMIC AREA, MALARIA OFTEN PRESENTS WITH ATYPICAL MANIFESTATIONS, SUCH AS

Atypical fever

In an endemic area, it is rather unusual to find cases with typical fever pattern. Some patients may not have fever at all and may present with other symptoms. Many present with fever of various patterns - low grade to high grade, with or without chills, intermittent to continuous, or even as cases of prolonged fever.

Headache

Headache may be a presenting feature of malaria, with or without fever. It can be unilateral or bilateral. Some times the headache could be so intense that it may mimic intra-cranial infections or intra-cranial space occupying lesions. It may also mimic migraine, sinusitis etc.

Body Ache, Back Ache and Joint Pains

These symptoms are fairly common in malaria. These can occur even during the prodromal period and at that stage these are generally ignored and diagnosis of malaria is impossible owing to lack of peripheral parasitemia. They are also common accompaniments of the malaria paroxysm. Sometimes, malaria may present only with these symptoms, particularly in cases of recurrent malaria.

Cough

Cough may be a presenting feature of malaria, particularly *P. falciparum* infection. Patient may have pharyngeal congestion and features of mild bronchitis. Patients who have persistent cough and/or fever even after clearance of parasitemia should be evaluated for secondary bacterial pneumonias/ bronchopneumonia and bronchitis.

Weakness

Sometimes patients may present with history of weakness, malaise. On examination they may have significant pallor, hypotension, dehydration etc. Algid malaria may present like this and the patient may not have fever *et al*l.

Hepatosplenomegaly

Patients can present with enlargement of liver and/or spleen, tender or non-tender, with or without fever. Rapid enlargement of spleen or liver in malaria can cause acute pain in the abdomen or chest. Generally, organomegaly is noticed in the second week of malarial illness. However, in cases of relapse or recrudescence, it may be present earlier. Although splenomegaly is a cardinal sign of malaria, absence of splenomegaly does not rule out the possibility of malaria.[9,12,18,21]

Malaria Control

Malaria continues to be a significant public health issue and a major hindrance to economic growth. Sustained control and management of malaria presents significant challenges. Effective interventions are available, these include widespread implementation of effective vector control and prompt and effective treatment with ACT following accurate diagnosis. Effective control and treatment of malaria presents enormous logistical challenges. The key to addressing the challenge of reducing the burden of malaria is an integrated approach that combines preventative measures, such as long-lasting insecticide-treated bed nets (LLINs) and indoor residual spraying (IRS), with improved access to effective anti-malarial drugs. However, malaria is a disease that stems from and causes poverty, and many at-risk populations live in extremely destitute, remote areas. Poor, rural families are the least likely to have access to these preventative measures that are fundamental to malaria control, and may live kilometres from the nearest healthcare facility. They are also less able to afford treatment once infection has occurred.[3,23]

The historic successful eradication of malaria in various parts of the world was achieved primarily by vector control, indicating that renewed efforts in this field, other than the current insecticide-based strategies, should be considered a central aspect of any malaria eradication strategy. However, given the increasing prevalence of mosquito resistance against the currently used chemicals, the need for development of new insecticides has high priority. Novel tools for the control of the adult mosquito include entomopathogenic fungi, insect-pathogenic viruses, the introduction of genetically engineered mosquitoes and the sterile insect technique (SIT).[19]

The development and spread of parasite resistance to certain anti-malarial agents has presented a major barrier to successful disease management in malaria-endemic areas, and has probably contributed to the resurgence of infection and the increase in malaria-related deaths in recent years. Resistance to almost all commonly used anti-malarials, notably chloroquine and sulphadoxine-pyrimethamine, but also amodiaquine, mefloquine, and quinine, has been observed in the most lethal parasite species, *P. falciparum*.[19,23]

Reducing malaria transmission by reducing gametocyte carriage with effective drugs can be an important factor in highly endemic areas. Some endemic countries are forging a path in malaria control and prevention using combined interventions and have achieved significant reductions in malaria burden. However, factors such as patient access to effective treatments and preventative measures, availability of training programmes and educational materials, and development and spread of resistance to certain anti-malarials are hindering progress. Addressing the continuing challenges presented by malaria in the years ahead will require responsive strategies such as innovative vector control methods, widespread implementation of biological diagnosis prior to treatment with effective anti-malarials, and close monitoring of local malaria epidemiology to identify areas of resurgence.[4,10,23]

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