PLASMODIUM INFECTION IN MAN: A REVIEW

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ABSTRACT

Plasmodium infection in man is caused by the bite of an infected female Anopheles mosquito. This results in the disease, malaria. Malaria has serious debilitating effects on man. It adversely affects man's health, strength and productivity. Here, a review of Plasmodium infection in man including the life cycle, transmission, immunity, symptoms, diagnosis, pathology, prevention, control and treatment is given. Only by knowing about Plasmodium infection, the burden of infection on man and the prevention and control options can we understand the disease better and so be better prepare for the future management of this disease.

Keywords: *Plasmodium* infection, Malaria, Epidemiology, Symptoms, Treatment, Control, Man

INTRODUCTION

Plasmodium causes malaria in humans. Malaria parasites (*Plasmodium*) are parasitic protozoan belonging to the sub-class, coccidia, and family, Plasmodiidae (Smyth, 1996). The female *Anopheles gambiae* mosquito is responsible for transmitting *Plasmodium* parasites. Malaria is a major public health problem with an estimated two million children worldwide dying of malaria yearly, primarily because of *Plasmodium falciparum* and its complications (Krogstad, 1996). Malaria is reported to be responsible for 500 million clinical cases and 2.7 million deaths each year (WHO, 1996b). Sub-Saharan African region has the greatest number of people exposed to malaria transmission and the greatest number of morbidity and mortality in the world (WHO, 1996a). The high-risk groups include young children, pregnant women, non-immune travelers, refugees, displaced persons and labourers entering endemic areas (Russel and Howson, 1996). It is estimated that in Africa, malaria is responsible for over one million deaths yearly of infants and young children (Angyo *et al.,* 1996). According to David (2000), every thirty seconds, a child somewhere dies of malaria. The loss of the daily labour cost coupled with cost of treatment and high mortality associated with the disease make malaria one of the main factors retarding development in Africa (Mutero *et al.*, 1998). By adversely affecting people's health, strength and productivity, malaria further marginalizes and impoverishes them (David, 2000). In Nigeria, malaria is hyper-endemic with stable transmission (Ofovwe and Eregie, 2001).

The global effects of the disease threaten public health and productivity on a broad scale and impede the progress of many countries toward democracy and prosperity (Oaks *et al.*, 1991). In spite of control programmes in many countries, malaria continues to be one of the world's greatest killers (WHO, 1989).

Malaria in humans is caused by four species of parasitic protozoan namely: *Plasmodium falciparum, P. vivax, P. malariae* and *P. ovale*. *P. malariae* has lost whatever predominance it may once have had and *P. vivax* and *P. falciparum* are the most commonly encountered malaria parasites worldwide (Carter and Mendis, 2002). However, *P. falciparum* is the most dangerous malaria parasite and causes most deaths (Oaks *et al.*, 1991). Because of the temperature preference on its transmission, *P. falciparum* is normally present in the tropical, sub-tropical and warm temperate regions. In the tropics, *P. falciparum* account for over 80 % of malaria cases (Carter and Mendis, 2002). The four species of *Plasmodium* that infect man result in four kinds of malarial fever. *P. falciparum* results in tropical malaria, *P. vivax* causes tertian malaria, and *P. malariae* causes quartan malaria, while *P. ovale* results in ovale tertian malaria (Smyth, 1996). The four species of *Plasmodium* differ morphologically and this can be used as a criterion for identification and diagnosis of malarial type.

MATERIALS AND METHODS

A comprehensive literature search was made from the Internet and serial materials of Nnamdi Azikiwe Library, University of Nigeria, Nsukka. Various journal articles, proceedings of learned societies of parasitology, WHO documents and textbooks were consulted vis-à-vis of the biomedical and socio-economic impact of plasmodium infection in man.

RESULTS

Life Cycle of Malaria Parasite: Although the life cycles of the four species of human malaria parasites are not identical, they are sufficiently alike to permit a general description. The life cycle of *Plasmodium* parasites can be divided into three stages; the exo-erythrocytic or pre-erythrocytic stage which usually occurs in the liver, the erythrocytic stage which occurs in the erythrocytes, and the sexual stage which occurs in the mosquito (Figure 1). In exo-erythrocytic stage, an infected female anopheline

mosquito introduces sporozoites into man during feeding. These sporozoites are taken up by the blood stream and within thirty minutes, they disappear from the blood stream. The sporozoites are elongate bodies measuring about 11μm in length, with a central nucleus. The sporozoites enter the liver cells (hepatocytes) where they develop to form cryptozoites. These give rise to metacryptozoites. This rapid multiplication by schizogony is referred to as pre-erythrocytic schizogony.

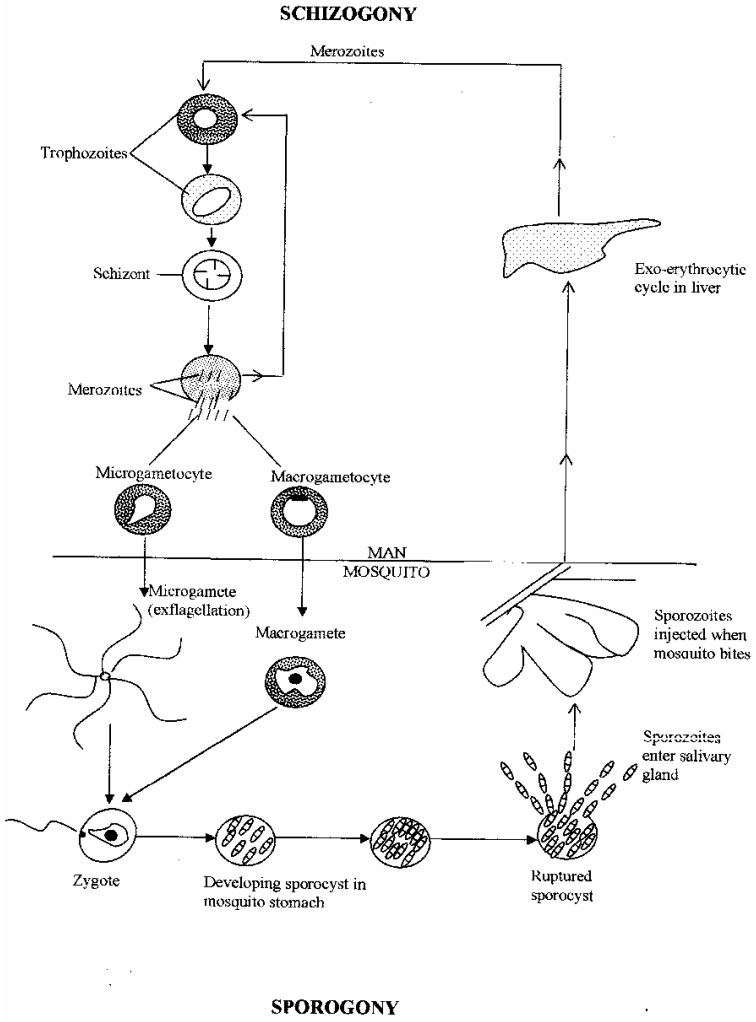

Figure 1: Generalized life cycle of malarial parasite (Mehlhorn and Walldorf, 1988)

By repeated divisions, over a period of six to nine days, metacryptozoites produce thousands of merozoites which are discharged into the blood circulation. In *P. vivax* and *P. ovale,* some injected sporozoites may differentiate into stages called hypnozoites which may remain dormant in the liver cells for sometime only to undergo schizogony causing relapse of disease when the red cells are invaded (Smyth, 1996). The life cycles of the species of *Plasmodium* affecting man are shown in Figure 2.

During the erythrocytic stage, merozoites enter into the erythrocytes. According to Aikawa (1980), entry of merozoites into a new erythrocyte is by a process called endocytosis. Endocytosis involves recognition and attachment of the merozoite to the erythrocyte membrane. On entry into an erythrocyte, a merozoite assumes the appearance of a small chromatin mass situated at the periphery of a larger mass of cytoplasm, in which a vacuole appears. Because of its characteristic appearance, this early trophozoite stage is referred to as a "signet ring". As it grows into maturity, it assumes an amoeboid shape as its nucleus divides to form up to 20 or more merozoites, depending on the *Plasmodium* species. The dividing stage is called a schizont. The mature schizont often called a segmenter causes the infected erythrocyte to rupture, thus releasing its merozoites into the blood stream. The merozoites within the blood attack new red blood cells thus repeating the erythrocytic schizogony cycle. The schizont also releases pigments and waste products which along with the merozoites are responsible for the feverish condition depicted by high temperature. Merozoites of some *Plasmodium* species show a distinct preference for erythrocytes of certain age. For instance, merozoites of *P. vivax* attack young immature red blood corpuscles called reticulocytes, those of *P. malariae* attack the older erythrocytes while those of *P. falciparum* indiscriminately enter into any available erythrocyte (Aikawa, 1980). After several generations of erythrocytic schizogony, some merozoites re-enter into red blood cells and develop into the sexual stages (sexual gametocytes) instead of schizogony stages (asexual schizonts). The male cells (microgametocytes) and the female cells (macrogametocytes) circulate in the blood until they either perish or are ingested by a female anopheline mosquito. The stage in the mosquito begins when a female anopheline mosquito feeds on infected blood, ingesting all the *Plasmodium* stages present in the blood stream. However, only the gametocytes survive to establish the sporogony cycle in the mosquito. In the midgut of the mosquito, the macrogametocyte develops a small amount of chromatin, and is thus transformed into a macrogamete. Equally in the mosquito midgut, the microgametocyte develops four to eight hair-like flagella (exflagellation) and is transformed into microgamete. The microgametes detach themselves and swim freely about in the fluid filled lumen of the midgut until they contact a macrogamete. Penetration is quickly accomplished. The fertilized macrogamete called a zygote develops into a mobile ookinete.

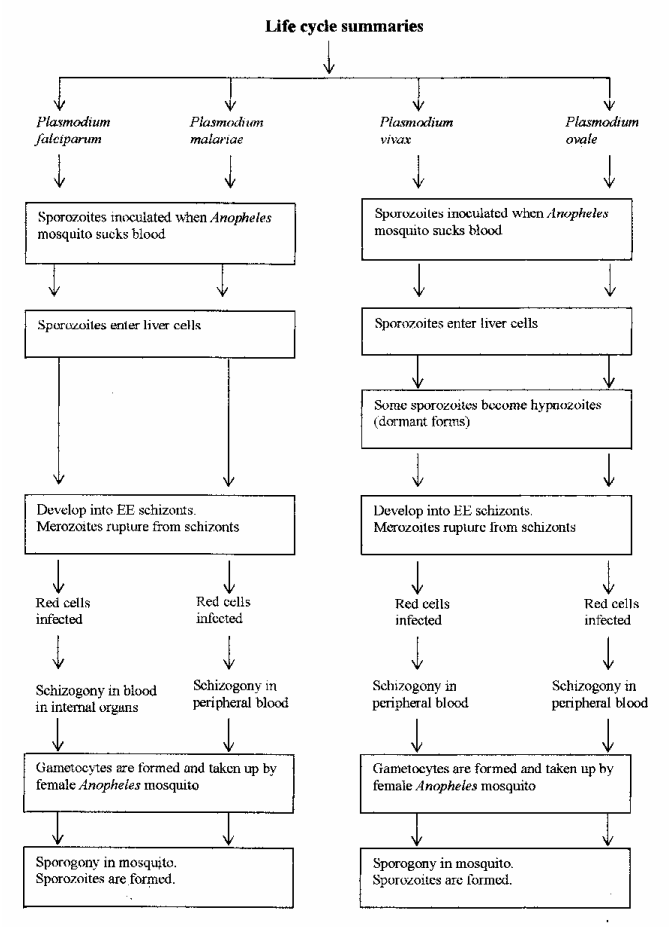

Figure 2: Life cycle of plasmodium species affecting man

The ookinete penetrates the stomach wall of the mosquito between the cells and develops as an oocyst. The oocyst gradually matures producing a spherical mass within which sporozoites develop mitotically. The oocyst usually matures in 10 – 20 days depending on temperature, *Plasmodium* species and physiological characteristics of the anopheline mosquito, attending a body size of 50 – 60μm. On rupture of the mature sporocyst, the sporozoites are released into the body cavity where they make their way to the salivary gland. On feeding, the sporozoites are injected into the tissues or directly into the blood stream of the new host (man) to initiate a new schizogony cycle.

Transmission of Malaria: Malaria is transmitted in various ways; by mosquito injection of sporozoites, by the transfer of erythrocytic stages other than gametocytes, and in a blood transfusion. Furthermore, blood donation from semi-immune persons without clinical symptoms may contain malarial parasites. In congenital malaria, infected mothers transmit parasites to their children before or during birth (Hoffman, 1996).

Malaria transmission in an area may be stable or unstable (WHO, 1996a). Stable malaria occurs when a population is continuously exposed to a fairly constant rate of malarial inoculation, while unstable malaria occurs seasonally with marked changes in transmission from one season to another and from one year to the other (Carter and Mendis, 2002). According to Carter and Mendis (2002), the differences in stability of malaria transmission, notably between tropical Africa and most other malarious regions are due largely to the behaviour and other biological characteristics of the regional species and sub-species of *Anopheles* vectors, and to their environment. The strong human - biting preferences and highly domestic habits of the tropical African vectors lead to very uniform contact between them and the human blood source in sub-Saharan Africa (Bruce-Chwatt *et al.*, 1966; Coluzzi, 1999). The climatic conditions are also highly conducive to malaria transmission, being warm and humid with relatively few fluctuations. This supports longevity of the vector mosquitoes and rapid development of the parasites within them (Oaks *et al.*, 1991). All of these features enable stable and indeed, generally intense malaria transmission in the tropics, notably Africa (Carter and Mendis, 2002).

Immunity to Malaria: Man's present understanding of immune mechanisms comes from observations made in infected people, from *in vitro* studies, and from experimental work carried out in laboratory systems (WHO, 1990). Immunity is usually established in stable malaria while immunity is unable to reach a high level in unstable malaria (Coluzzi, 1999). There are two types of clinical immunity, one, which reduces the risk of death from malaria, and another, which reduces the intensity of clinical symptoms. A third type is antiparasitic immunity, which directly reduces the numbers of parasites in an infected individual (Carter and Mendis, 2002). The number of malarial inoculations experienced and the intervals between them are all important to the malaria immune status of an individual. In the case of acute attacks of *P. falciparum* malaria, it is possible that a degree of immunity to some aspects of severe life-threatening disease may be achieved after only one or two infections (Gupta *et al.*, 1999). However, clinical immunity to other non life-threatening clinical effects of malaria requires more and frequent inoculations of malaria (Trape and Rogier, 1996). Because of the time taken to achieve effective immunity to malaria under conditions of endemic infection, antimalarial immunity is often said to be "age dependent". Very young children appear to have a poor capacity to acquire effective protective antimalarial immunity of any sort, while older children and adults may do so more readily (Baird *et al.*, 1991; Baird, 1995).

Symptoms: Symptoms of *P. falciparum* infection may include fever, chills, sweats, cough, diarrhea, respiratory distress and headache (UACHPPM, 2004). Symptoms of infection with *P. vivax, P. malariae* or *P. ovale* may begin with indefinite malaise and a slow rising fever several days in duration, followed by shaking chills and rapidly rising temperature, usually

accompanied with headache and nausea, and ending with profuse sweating. After a period free of fever, the cycle of chills, fever and sweating is repeated every one to three days (Cheesbrough, 1987).

Diagnosis: Diagnosis of malaria is accomplished through the demonstration of the malaria parasites in blood films, which could be either thick or thin. Other supportive techniques include sophisticated indirect fluorescent antibody (IFA) test, immunoglobulin values and haemagglutination tests (UACHPPM, 2004). Over the last few years, several malaria rapid tests have been developed which make a rapid diagnosis possible. They require a drop of blood from a finger prick, and involve a paper test strip that is dipped into the blood and other solution(s). After a few minutes, during which the liquids are absorbed into the strip, a reading is obtained by the presence or absence of a coloured test line on a white background (MRC, 2001).

Pathology: *Plasmodium* infection has several effects on man. It can cause anaemia and this can be severe particularly in young children. Severe anaemia exerts a heavy toll on African children in malaria endemic countries. A recent estimate suggests that approximately 1.4 - 5.7 million cases occur each year, killing 190,000 – 974,000 children less than 5 years of age, with the highest mortality occurring in infants less than 12 months old (Murphy and Breman, 2001). Blackwater fever and cerebral malaria also results from *Plasmodium* infection. Other effects are diarrhoea and vomiting, especially in children, pulmonary oedema which is rare but often fatal, and hypoglycaemia which is being increasingly reported in patients with severe malaria, especially children and pregnant women (WHO, 1986a; Murphy and Breman, 2001).

DISCUSSION

Prevention and Control: It is recommended by World Health Organization (WHO) that malaria control should be based on an epidemiological approach and that it should be planned and coordinated within primary health care with the active participation of the community (WHO, 1986b). There are two goals in the management of malaria; treating the sick and reducing the risk of malaria (WHO, 1993). Treating the sick is entirely dependent on the effective use of antimalarial drugs delivered to malaria patients in a timely manner. To achieve this, health delivery systems will have to be vastly improved, especially in most of tropical Africa (Gilson and Mills, 1995).

In reducing the risk of malaria, several methods are used. These methods include, especially in Africa, the expanded deployment and use of insecticide-treated materials, bed-nets, and curtains for those at highest risk namely, infants, young children and pregnant women (Guillet *et al*., 2001; N'Guessan *et al*., 2001). In controlled experimental trials, increased survival rates among African children sleeping under insecticide-impregnated bed-nets, (IBNs) have been consistently reported (Alonso *et al*., 1991; Binka *et al*., 1996; Curtis, 1996; Nevill *et al*., 1996). This is probably because in very young children in whom significant levels of immunity have not yet developed, protection against the sheer numbers of malaria attacks that IBNs would afford reduces the risk of a fatal infection at this very vulnerable age (Alles *et al*., 1998).

Other strategies aimed at reducing malaria transmission are the genetic manipulation of mosquito vectors (Clarke, 2002; CNN, 2002; Holt *et al*., 2002; Hoffman *et al*., 2002a; NS, 2004). Researchers at Case Western Reserve University School of Medicine created a gene called SM1, which encodes for a protein that interferes with the development of the parasite in the mosquito (SABIC, 2002). These mosquitoes have not yet been released in an attempt to replace infectious populations, as more research is required. The use of genetically modified insect vectors in the field will require considerations in terms of biosafety, ecology, ethical, legal and social issues. The genome sequence of *Anopheles gambiae* provides an architectural scaffold for mapping, identifying, selecting and exploiting desirable insect vector genes (SABIC, 2002).

The development of a transmission – blocking vaccine is another strategy aimed at reducing malaria transmission (Meuwissen, 1989; Russel and Howson, 1996; Arnot *et al*., 1998). In their work, Florens *et al*. (2002) applied a high-throughput proteomics approach to identify new potential drug and vaccine targets and to better understand the biology of *P. falciparum*. They detected chromosomal clusters encoding co-expressed proteins, which suggested a potential mechanism for controlling gene expression. DNA vaccines and recombinant viral vector vaccines are now at the pre-clinical and clinical testing stages at various centers (Webster and Hill, 2003). DNA vaccines are effective at priming cellular immune responses, which are likely to be important in liver-stage malaria. Pre-erythrocytic vaccines are an attractive prospect, as they would prevent the invasion of hepatocytes by sporozoites or destroy parasites in infected hepatocytes and would thus prevent both clinical disease and the transmission of malaria. There is evidence that vaccination with irradiated sporozoites, which abort their development at the liver stage, can lead to protection of up to 90 % of immunized human volunteers following a regime involving the bites of more than 1000 irradiated infected mosquitoes over a period of time (Hoffman *et al*., 2002b). Probably the best characterized pre-erythrocytic antigen is the circumsporozoite protein (CSP) which is expressed on the extracellular sporozoite and the intracellular hepatic stages of the parasite (Malik *et al.,* 1991). The development of blood-stage vaccines has been focused on targeting the antigens responsible for parasite entry into cells. The best characterized antigen is MSP1, a major surface merozoite protein (Cheng *et al*., 1997). Transmission-blocking vaccines (TBVs) against malaria are intended to induce immunity against the stages of the parasite that

infect mosquitoes so that individuals immunized with TBVs cannot transmit malaria. These vaccines target the sexual stage of the malaria parasite with the aim of generating antibody responses that inhibit exflagellation and fertilization of the parasites in the mosquito vector. As a result, such vaccines would not have any effect on the clinical manifestations of malaria in an individual, but could have major impact through reducing malaria transmission and thus malaria mortality and morbidity at the population or community level (Russel and Howson, 1996). TBVs against the two major species of human malaria parasite, *P. falciparum* and *P. vivax* are under development (Carter, 2001).

Appropriate construction and siting of housing and local environmental improvement which includes destruction of breeding places of mosquitoes by draining gutters properly and keeping grasses around the home low can also help in reducing human-mosquito contact. Monitoring, including by satellite, of all aspects and features of a malarious situation will be important to the timing and targeting of antimalarial interventions (Thomson and Connor, 2001). According to Kishore (2002), Remote Sensing Technologies through satellites is likely to become a rapid epidemiological tool for surveillance of vector borne diseases and malaria in particular.

The Roll Back Malaria (RBM) initiative is another measure aimed at the control of malaria. RBM is unique in that, unlike previous global campaigns against malaria, it focuses on building sustainable community capacity and also, it raises the level of political commitment and advocacy at the country level (David, 2000; Saiprasad and Benerjee, 2003). Priority areas of RBM include the improvement of health systems, disease management, provision of anti-malarial drugs and malaria related control materials, disease prevention, disease surveillance and epidemic detection and control, sustainable control, human resources development and research including inter-disciplinary operational research (WHO, 2005). The goal of RBM is to provide reliable information on progress in controlling malaria that can be used at local and national levels and can inform regional and global efforts. RBM aims to control malaria to a level where it is no longer one of the major contributors to mortality and morbidity (David, 2000).

Treatment: Treatment of malaria could be supportive or specific. Supportive treatment include measures designed to combat the anaemia, reduce fever and maintain proper hydration and nutrition while specific treatment depends on accurate diagnosis and a thorough knowledge of the actions of the antimalarial drugs. Two types of drugs are used to treat malaria; blood schizonticides and tissue schizonticides (UACHPPM, 2004). Blood schizonticides attack the parasites within red blood cells. They are used in acute infection to prevent or terminate the clinical attack. Examples include amodiaquin hydrochloride, chloroquine phosphate, chlorguanide and quinine. However, the resistance of *P. falciparum* malaria to chloroquine has been widely reported (Neequaye *et al*., 1986; Rathod *et al*., 1997; Peters, 1998; Warhurst, 2001). Here in Nigeria, resistance to chloroquine has also been reported (Umotong *et al*., 1991; Sowunmi and Salako, 1992; Molta, 1995; Erah *et al*., 2003). Hence, scientists are still carrying out research on new and more effective antimalarials. Tissue schizonticides on the other hand act on the exo-erythrocytic parasitic stages in liver cells to prevent a relapse. They include drugs like primaquine phosphate, pamaquine, and pyrimethamine. Recently, aertemisinin and its derivatives from a Chinese herb have held out a great promise in the fight against malaria (Ezigbo, 1990).

Conclusion: The knowledge about *Plasmodium* infection will go a long way in reducing the prevalence of infection in man. Overall, it can be said that the impact of malaria on man has been very great. In one way or the other, the burden of malaria continues to this day at an unacceptable level.

In the future management of malaria, the tools available, drugs, insecticides, insecticide-treated materials, etc. will be of great importance. They are, individually and collectively, very effective instruments, although they are under constant threat from drug-resistant parasites and insecticide-resistant vectors. To maintain these tools, sustained investment of effort and resources is required on a much greater scale than is taking place at present. This could happen only in the presence of the necessary economic, political and social development in all of the affected countries.

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