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Exploring The Basics of The Malaria Burden For Eradication Strategies

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ABSTRACT

Malaria infection is a public health problem of global concerns. Malaria is an endemic disease in major areas of Africa and some part of America and Asia. Typical symptoms of malaria include headaches, fever, vomiting, rigors, chills and tiredness while severe malaria could lead to seizures, coma, severe anaemia, respiratory distress, convulsions, hypoglycemia, yellow skin or death. Effective management of malaria begins with an accurate diagnosis of the disease. Identification of malaria parasites or antigens are used for malaria diagnosis. An understanding of the plasmodium's metabolism could be explored to develop new therapeutic strategies. However, there were observable resistances noted in *P. falciparum*, which, continually threatens their efficacy and has necessitated the need new antimalarial combinations and the discovery, design and development of new drugs.

Keywords: Malaria; plasmodium; infection, endemic; antimalarial.

1. INTRODUCTION

Malaria, which is referred to as the "King of Diseases", has resulted in a disturbing global health problem. This infectious disease has affected over 3 billion people with about 100 countries (Figure 1) at risk (WHO, 2015). Typical symptoms of malaria include headaches, fever, vomiting, rigors, chills and tiredness while severe malaria could lead to seizures, coma, severe anaemia, respiratory distress, convulsions, hypoglycemia, yellow skin or death (Caraballo, 2014). Observable symptoms in persons bitten by the infected mosquito are noticed usually from day ten to fifteen after bite. There could also be recurrences of the diseases months after if not properly treated (WHO, 2015). Plasmodium, an obligate erythrocytic protozoa is the causative agent of malaria. Different species of malaria parasites that infect humans include *P. falciparum, P. malariae, P. vivax* and *P. ovale*. Infections can occur through a female anopheles mosquito bite that transmits plasmodia, by congenital transmission and exposure to infected blood (Figure 2). Plasmodium falciparum, *a* drug-resistant *specie causes severe and life*-threatening forms of malaria, which continues to spread almost throughout the world (Naing, et al., 2014). Most cases of malaria in developed countries occur usually among immigrants, military personnel or travelers from endemic areas (Ahmed and Cox-Singh, 2015).

In spite of recent developments towards eliminating malaria in some countries especially in Africa, Asia and South America, this disease has remains a major health challenge in countries with a weak healthcare system (White et al., 2014). Since the millennial, there has been significant investment in novel tools to combat malaria. Although the

challenges involving the use of these new tools are that they are expensive, complex technologies or still under trial (Gonçalves and Hunziker, 2016). The readily available tools include rapid diagnostic tests, insecticidal bed nets, and artemisinin-based combination treatment (ACT). To effectively control and eliminate malaria, there is need for early identification and treatment of infected persons and it is therefore important that people in the endemic area have easy access to reliable diagnostics and effective treatment.

2. EPIDEMIOLOGY OF MALARIA

According to WHO, there were about 210 million new recorded cases of this infectious disease and around 450,000 deaths (WHO, 2015). About 70% of these cases occurs in children below the age of 15 while over 120 million pregnant women are at risk yearly of the infection (Murray et al., 2012). Malaria is currently an endemic disease in many nations of Africa and some part of America and Asia (Figure 1). An estimated report in 2009 revealed that countries with high mortality rate per 100,000 of population were Ivory Coast (86.15), Angola (56.93) and Burkina Faso (50.66) (Provost, 2011). Topical areas have high malaria prevalence because of rainfall with consistent high temperatures and humidity, and stagnant waters; a good condition for mosquitoes to breed (Jamieson et al., 2006).

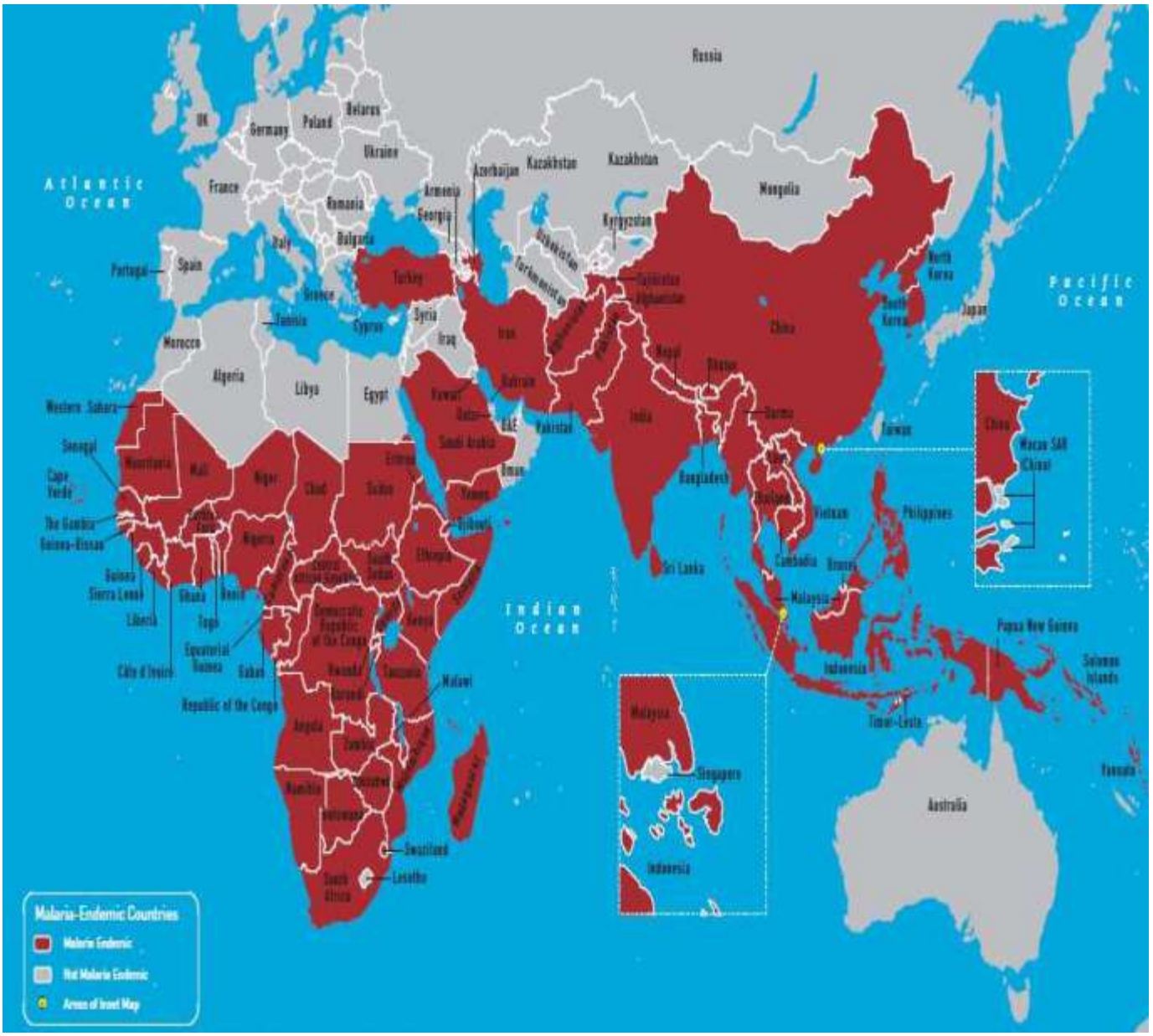

Figure 1: Malaria-Endemic Countries

Source: Center for Disease Control (CDC),https://www.cdc.gov › travel-static › yellowbook › map_3-10, Accessed on August 29, 2019.

3. THE LIFE CYCLE OF *P. falciparum*

(A) The first stage in the life cycle of *P. falciparum* involves a feeding female anopheline mosquito injecting sporozoites (spzs) into the dermis of human.

(B) The injected sporozoites are transported to the hepatocyte via vasculature. Before locating a suitable hepatocyte, there is usually cellular traversal before active invasion. Numerous daughter merozoites are released into the vasculature.

(C) They interact with the erythrocytes for the initiation of asexual cycle of schizogony in the blood

(D) A fraction of merozoites are reprogrammed to go through gametocytogenesis.

(E) The sequestering and development of gametocytes within the bone marrow within a 15-day period occur in this stage, and they become mature. They can then enter the circulation for ingestion where they develop into male and female gametes in the midgut.

(F) Zygote are formed through mating by fusing of gamete and it is transformed into a ookinete over 24 hours that goes through the mosquito midgut encysts and epithelium to become an oocyst where sporogenic replication occurs (Lacerda et al., 2012).

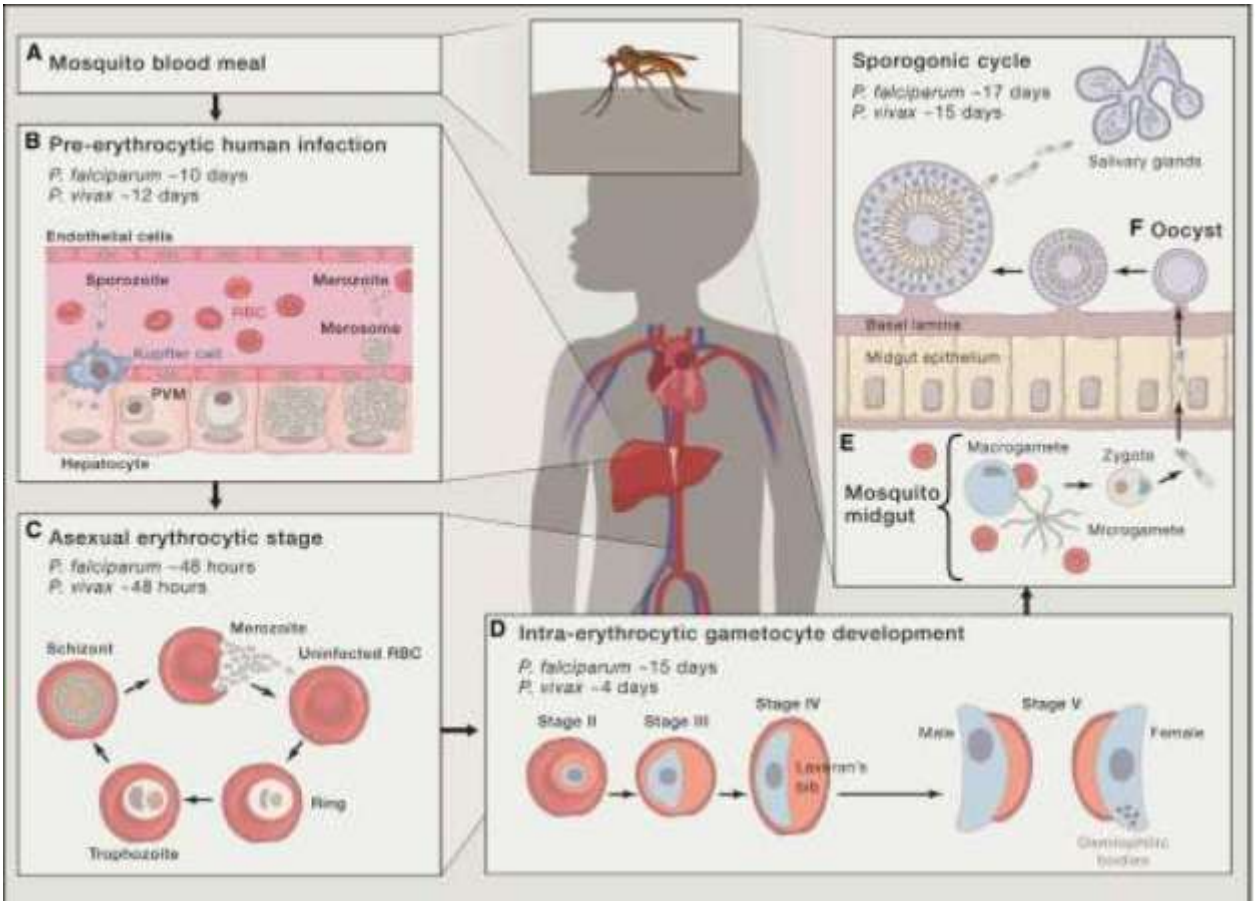

Figure 2: The Life Cycle of *P. falciparum*

4. BIOCHEMISTRY OF PLASMODIUM INFECTION

Malaria parasite undergoes rapid multiplication rate during the different stages of its life cycle. Therefore, the need for energy through metabolism of the different biomolecules cannot be over-emphasized, as it is required for survival and reproduction. The host-parasite interactions also enhance the parasite's metabolism. An understanding of the plasmodium's metabolism could be explored to develop new therapeutic strategies.

The primary source of energy for the parasite is glycolysis. This metabolic step involves converting glucose to lactate (glycolysis) catalyzed by Lactate dehydrogenase. They display increased glycolytic rate, over 70 times more than uninfected erythrocytes. High Lactate dehydrogenase (LDH) activity is essential for NAD+ regeneration from NADH initially produced during the formation of glyceraldehyde-3-phophate dehydrogenase. Some glycolytic intermediates

are diverted to the pentose phosphate pathway for the synthesis of ribose sugars needed for nucleotide metabolism and NADPH regeneration.

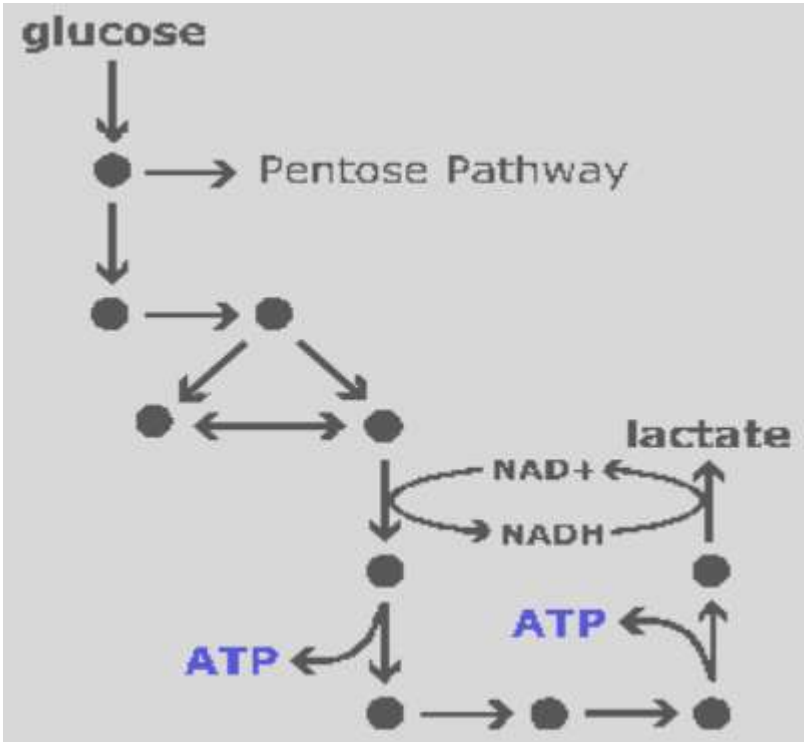

Figure 3: The glycolytic pathway

The parasite's membranes are made up of lipids. There is need for more lipid during the life cycle of plasmodium for the membrane's surface area and volume. Targeting the lipids metabolism due to the huge demand for lipid for anti-malarial drugs can be explored (Mitamura and Palacpac, 2003)

For nucleotides of the parasite such as DNA and RNA, they are composed of ribose sugar group bounded to a phosphate group and a purine (guanine and adenine) or a pyrimidine (cytosine, thymine and uracil) base. The bases can be synthesized either via de novo pathway (pyrimidine) or by the salvage pathway (Purine).

5. DIAGNOSIS

Effective management of malaria is preceded by a prompt and accurate diagnosis of the disease. Diagnostic schemes are emerging due to the global impact of malaria in developed areas where expertise is often lacking and in resource-limited areas with substantial burden (Reyburn et al., 2007). Identification of the malaria parasites or antigens are used for malaria diagnosis. The efficacy of the process is dependent on some factors such as the species, drug resistances, parasitemia and the use of chemoprophylaxis. Malaria is a potentially deadly disease and should be diagnosed and treated early to avoid death (Ahmed and Cox-Singh, 2015).

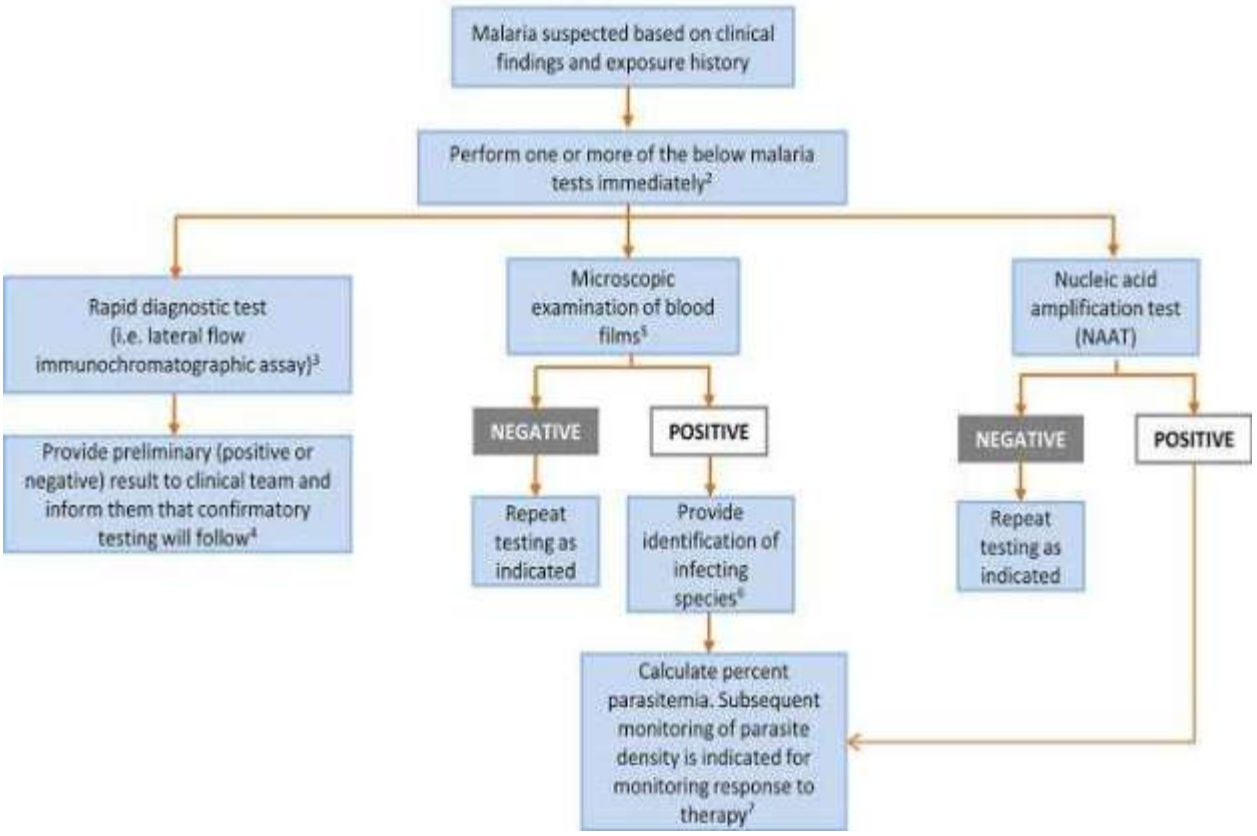

Figure 4: Malaria laboratory testing algorithm

Clinical diagnosis is the most widely practiced and less expensive. It is based on symptoms and findings observable during physical examination (Lacerda et al., 2012). Its challenges is the non-specific nature of the signs and symptoms (McMorrow et al., 2008) Laboratory diagnosis of malaria involves different techniques like microscopic blood diagnosis (Ngasala et al., 2008), rapid diagnostic tests (Tagbor et al., 2008), molecular methods using polymerase chain reaction (PCR) (Vo et al., 2007).

6. TREATMENT

The use of quinine from the cinchona tree was one of the foremost antimalarial drug and since then malaria treatment has been mainly antimalarial drugs to control and prevent against malaria. After Quinine, many drugs were developed in the 20th century for example, artemisinin and chloroquine. However, there were observable resistances in *P. falciparum*, which continually threatens their continuing efficacy thereby providing for increased antimalarial combinations as well as developing new drugs and novel targets. In response to drug- resistance, artemisinin-based combination therapies (ACTs) are now recommended for treatment of uncomplicated malaria Dondorp et al., 2009).

7. ANTIMALARIAL DRUGS: FROM THE PAST TO THE FUURE

The first chemically purified effective treatment for malaria was quinine, isolated from the bark of the cinchona tree in 1820. This drug is still effective until today (Achan et al., 2011, Tse et al., 2019). Mepacrine (also called quinacrine) was mainly used as a prophylactic during World War II (Tse et al., 2019, Green, 1932). Chloroquine was used to cure different strains of the malaria parasite in the 1940s (Tse et al., 2019, Loeb, 1946). Mefloquine was invented in the 1970s by the US Army and exist until today (Tse et al., 2019, Trenholme, 1975). The Walter Reed Army Institute of Research developed halofantrine between 1960s and 1970s (Tse et al., 2019, Cosgriff et al., 1982). Artemisinin was first isolated from the plant Artemisia annua, an herb that has commonly been used in Chinese traditional medicine in 1971 by Tu Youyou (Tse et al., 2019, Qinghaosu Antimalaria Coordinating Research Group, 1979). Artemisinin has been shown to be efficacious against all multi-drug resistant forms of *P. falciparum*. The most common derivatives of artemisinin are artemether, artesunate and arteether (Tse et al., 2019). High-throughput screens have identified many new chemotypes that have been developed into highly promising anti-malarial candidates. Most of these compounds have showed novel mechanism of actions that are essential for these future drugs to succeed. The discovery of these novel mechanisms of actions will make the development of future anti-malarials possible (Tse et al., 2019).

8. CONCLUSION

Although, there have been increased effort towards the eradication of malaria parasites especially in the endemic area, the necessary diagnostics tools should be readily available with trained personnel to handle them. The government of such area should put in more effort to ensure the complete elimination of this infection.

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