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A DIMINUTIVE ASSESSMENT OF ANTIMALARIA THERAPIES THUS FAR

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Abstract

Malaria is caused by the plasmodium species of protozoan parasites namely; *Plasmodium falciparum, Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium vivax* and *Plasmodium knowlesi*. Common symptoms of malarial infection include headache, vomiting, high fever, convulsions, among others. The aim of this review is to study and arrange the different classes of malarial drugs, their mechanism of action, therapeutic activities and structures; and also their merits. Some of the drugs reviewed are; chloroquine, artemether, amodaquine, lumapil, oraxyl, and fansidar among others. During the course of this review, artemisinin derivatives class of antimalaria drug was reported to kill parasite more rapidly than other conventional anti malarial drugs and are active against both sexual and asexual stages of the parasite cycle, they are also more rapidly eliminated than others i.e. has a short half life and has a widespread application with less adverse effect when taken within the therapeutic dosage. It is therefore suggested that improvement be made on the classes to enhance their therapeutic index.

Keywords: *Malaria; plasmodium; antimalarial drug; artemisinin*

Introduction

Malaria is a life threatening protozoan disease caused by malaria parasites belonging to the *genus Plasmodium.* The malaria parasites that infect humans belong to four species: *Plasmodium.*

P. falciparum, *P. vivax, P. malariae and P.ovale.* While these four species do not ordinarily infect animals; there is evidence that Chimpanzees may act as a reservoir host for *Plasmodium malariae* in Africa, providing a possible source of human infection (Arora and Arora, 2009).

Malaria is a common and life-threatening disease in many tropical and subtropical areas. There are currently over 100 countries and territories where there is a risk of malaria transmission, and these countries are visited by more than 125 million international travelers every year, making the transmission a certain possibility (Arora and Arora, 2009).

Annually, many international travelers fall ill with malaria while visiting countries/territories where malaria is endemic, and well over 10 000 are reported to become ill with malaria after returning home; however, underreporting means that the real figure maybe considerably higher. International travellers to countries/territories with ongoing local malaria transmission arriving from countries with no transmission are at high risk of malaria infection and its consequences because they lack immunity. Migrants from countries/territories with malaria transmission living in malaria-free countries and returning to their home countries to visit friends and relatives are similarly at risk because of waning or absent immunity. Travellers who fall ill during travel may find it difficult to access reliable medical care, and those who develop malaria upon returning to a country that is malaria-free face particular problems: medical personnel may be unfamiliar with malaria, the diagnosis may be delayed, and effective antimalarial medicines may not be registered and/or available, resulting in progression to severe and complicated malaria and, consequently, high case fatality rates (Arora and Arora, 2009). Fever occurring in a traveller within 3 months of leaving a country in which there is risk of malaria is a potential medical emergency and should be investigated urgently to exclude malaria. In the absence of rapid access to reliable diagnostic facilities, stand-by emergency treatment is indispensable.

1.0 Historical Perspective

Malaria is an old disease whose name is derived from the Italian (mal-aria) or "bad air" and it was also known as Roman fever, ague, marsh fever, and periodic fever (Paludism, 2003). There were numerous, sometimes bizarre theories on how malaria was transmitted until 1898 when Dr. Ronald Ross discovered that the female Anopheles mosquito was actually responsible for transmitting malaria parasite. This discovery revolutionized malaria control, which had hitherto often been haphazard or based purely on treating the patient by killing the malaria parasites (Phillips, 2001, Cheesbrough, 2006, Arora and Arora, 2008). Malaria probably originated in Africa and accompanied human migration to the Mediterranean shores, India and South East Asia. In the past it used to be common in the marshy areas around Rome. As malaria is a disease mostly of tropical and subtropical areas, it is particularly prevalent in sub-Saharan - Africa, but also common throughout other tropical regions of China, India, Southeast Asia, South and Central America. (Cheesbrough, 2006, Arora and Arora, 2008)

In Nigeria, before independence, the colonialists established Government Reservation Areas (GRA) in an attempt to build their homes far away from the natives as it was found that the travelling/flying distance of these mosquitoes from the breeding grounds was a limiting factor in spreading the parasites. Nigeria's quest for effective control of malaria began well before the World Health Organization (WHO) global malaria eradication period between 1955 and 1968 (Gilles *et.al,* 2007).

From 1955, however, a more focused egalitarian attempt at evolving strategic plans and interventions resulted in pre-eradication pilot studies such as the Kankiya District Project and the establishment of a division in Ministry of Health to deal with the mosquito and malaria problem.

The National Malaria Control Committee (NMCC) was set up in 1975 with the set mandate to reduce the malaria burden by 25%. It produced a five year plan of action that terminated in 1980 however; it recorded only modest achievements (Gilles *et.al,* 2007).

It took another 8 years before progress was made when a major health system reform was carried out in 1988, with the adoption of a Health Policy for the country. Within this Policy, malaria was to be eradicated using the concept of Primary Health Care. The ministry of Health subsequently prepared guidelines for malaria control in 1989. Government finally came out with a National Malaria Control Plan of Action 1996. Past and present malaria control programs as well as the most recent Malaria Control programme (Akanbi 2009).

Plan achieved limited success in eradicating the scourge. In spite of this, the malaria situation has steadily worsened and currently it is estimated that malaria accounts for 65 percent of all diseases reported in Nigerian health facilities and that 42% of pregnant women are diagnosed with malaria and affects the birth weight of infants (Akanbi 2009).

1.1 Epidemiological Data of Malaria

In Bangladesh, the malaria situation has been steadily deteriorating since the late 1980s. The number of cases increased fivefold between 1988 and 1994. In Latin America, Brazil is worst affected with over 50% of all malaria.

An estimate for 2009 reported that countries with the highest death rate per 100,000 of population were Ivory Coast (86.15), Angola (56.93) and Burkina Faso (50.66). 2010 estimates indicated the deadliest countries per population were Burkina Faso, Mozambique and Mali. The Malaria Atlas Project aims to map global endemic levels of malaria, providing a way to determine the global spatial limits of the disease and to assess disease burden. This effort led to the publication of a map of *P. falciparum* endemicity in 2010 (Carson *et al.,* 1998; WHO, 2012).

As of 2010, about 100 countries have endemic malaria (Arora and Arora, 2008). Every year, 125 million international travelers visit these countries, and more than 30,000 contract the disease.

In 2012, there were 207 million cases of malaria. That year, the disease is estimated to have killed between 473,000 and 789,000 people, many of whom were children in Africa. Efforts at decreasing the disease in Africa since the turn of millennium have been partially effective, with rates of the disease dropping by an estimated forty percent on the continent (WHO, 2012).

The WHO estimates that in 2015, there were 214 million new cases of malaria resulting in 438,000 deaths. Other epidemiologist estimated the number of cases at between 350 and 550 million for *P. falciparum* malaria. The majority of cases (65%) occur in children under 15 years old. About 125 million pregnant women are at risk of infection each year; in Sub-Saharan Africa, maternal malaria is associated with up to 200,000 estimated infant deaths yearly. There are about 10,000 malaria cases per year in Western Europe, and 1300–1500 in the United States. About 900 people died from the disease in Europe between 1993 and 2003. Both the global incidence of disease and resulting mortality has declined in recent years (WHO, 2015).

According to the WHO and UNICEF, deaths attributable to malaria in 2015 were reduced by 60% from a 2000 estimate of 985,000, largely due to the widespread use of insecticide-treated nets and artemisinin-based combination therapies. (WHO, 2015)

Malaria is presently endemic in a broad band around the equator, in areas of the Americas, many parts of Asia, and much of Africa; in Sub-Saharan Africa, 85–90% of malaria fatalities occur. The geographic distribution of malaria within large regions is complex, and malaria-afflicted and malaria-free areas are often found close to each other. Malaria is prevalent in tropical and subtropical regions because of rainfall, consistent high temperatures and high humidity, along with stagnant waters where mosquito larvae readily mature, providing them with the environment they need for continuous breeding. In drier areas, outbreaks of malaria have been predicted with reasonable accuracy by mapping rainfall. Malaria is more common in rural areas than in cities. For example, several cities in the Greater Mekong Sub region of Southeast Asia are essentially malaria-free, but the disease is prevalent in many rural regions, including along international borders and forest fringes. In contrast, malaria in Africa is present in both rural and urban areas, though the risk is lower in the larger cities (WHO, 2015).

Malaria is a public health problem today in more than 90 countries, inhabited by 2.4 billion people – 40% of the world's population. An estimated 300 to

500 million cases each year cause 1.5 to 2.7 million deaths, more than 90% of which occur in children under age 5 in Africa. Malaria kills one child every 30 seconds. Progresses made in the last 50 years in restricting the geographical areas affected by malaria are being eroded recently, due to changes in land use, global climate changes, and armed conflicts/movement of refugees, easy international travel and development of multi-drug resistant strains of parasite (WHO, 2015).

The vast majority of areas of endemic malaria show resistance to chloroquine (the oldest, cheapest treatment). Resistance to sulfadoxine-pyrimidine is emerging in most affected areas, resistance to mefloquine has also been observed in South-east Asia (areas of multi-drug resistance) (WHO, 2015).
Epidemiologists have recently paid greater attention than in the past to the epidemiology of clinical malaria as opposed to the epidemiology of malarial infection. This change of emphasis has been stimulated in part by the need for better clinical definitions of malaria in the evaluation of control measures such as insecticide-treated materials and malaria vaccines. Methods of determining mortality from malaria and of defining severe and uncomplicated malaria have been devised. The limited data available indicate that malaria-attributable mortality and the incidence of severe malaria do not increase with an increase in the entomological inoculation rate above a threshold value, an observation that has important implications for the likely long-term effects of attempts to contain malaria through vector control.

Study of the epidemiology of severe malaria in Africa has shown different epidemiological patterns for the two most frequent forms of this condition: cerebral malaria and severe malarial anemia; Severe malarial anemia is seen most frequently in areas of very high malaria transmission and most frequently in young children. In contrast, cerebral malaria predominates in areas of moderate transmission, especially where this is seasonal, and it is seen most frequently in older children. Study of patients with uncomplicated malaria has established the relationship between fever and parasite density and has demonstrated ways of defining fever thresholds. Algorithms have been developed to help in the diagnosis of malaria in the absence of parasitological confirmation but this approach has proved difficult because of the overlap in symptoms and signs between malaria and other acute febrile illnesses such as pneumonia (WHO, 2018).

Even though the malaria life cycle was discovered a century ago, new aspects of the epidemiology of the disease have recently been described. While early malaria surveys sought mainly to determine the extent of infection in given community, epidemiologists are now increasingly interested in the epidemiology of clinical malaria. This shift in focus was prompted partly by the need for better clinical definitions of malaria in evaluating control measures such as insecticide-treated materials and malaria vaccines. Available data indicate that malaria-attributable mortality and the incidence of severe malaria do not increase with an increase in the entomological inoculation rate above a threshold value. This observation has important implications for efforts to contain malaria through vector control.

In 2017, an estimated 219 million cases of malaria occurred worldwide (95% confidence interval [CI]: 203–262 million), compared with 239 million cases in 2010 (95% CI: 219–285 million) and 217 million cases in 2016 (95% CI: 200–259 million) (WHO, 2018). Although there was an estimated 20 million fewer malaria cases in 2017 than in 2010, data for the period 2015–2017 highlight that no significant progress in reducing global malaria cases was made in this timeframe. Most malaria cases in 2017 were in the WHO African Region (200 million or 92%), followed by the WHO South-East Asia Region with 5% of the cases and the WHO Eastern Mediterranean Region with 2%. Fifteen countries in sub-Saharan Africa and India carried almost 80% of the global malaria burden, with five countries accounted for nearly half of all malaria cases worldwide: Nigeria (25%), Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%). The WHO South-East Asia Region continued to see its incidence rate fall – from 17 cases of the disease per 1000 population at risk in 2010 to 7 in 2017 (a 59% decrease). All other WHO regions recorded either little progress or an increase in incidence rate. The WHO Region of the Americas recorded a rise, largely

due to increases in malaria transmission in Brazil, Nicaragua and Venezuela (Bolivarian Republic). In the WHO African Region, the malaria incidence rate remained at 219 cases per 1000 population at risk for the second year in a row (WHO, 2018).

Plasmodium falciparum is the most prevalent malaria parasite in the WHO African Region, accounting for 99.7% of estimated malaria cases in 2017, as well as in the WHO regions of South-East Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%). *P. vivax* is the predominant parasite in the WHO Region of the Americas, representing 74.1% of malaria cases Malaria deaths (WHO, 2018).

In 2017, there were estimated 435 000 deaths from malaria globally, compared with 451 000 estimated deaths in 2016, and 607 000 in 2010. Children aged less than 5 years are the most vulnerable group affected by malaria. In 2017, they accounted for 61% (266 000) of all malaria deaths worldwide. The WHO African Region accounted for 93% of all malaria deaths in 2017. Although the WHO African Region was home to the highest number of malaria deaths in 2017, it also accounted for 88% of the 172 000 fewer global malaria deaths reported in 2017 compared with 2010. Nearly 80% of global malaria deaths in 2017 were concentrated in 17 countries in the WHO African Region and India; 7 of these countries accounted for 53% of all global malaria deaths: Nigeria (19%), Democratic Republic of the Congo (11%), Burkina Faso (6%), United Republic of Tanzania (5%), Sierra Leone (4%), Niger (4%) and India (4%). All WHO regions except the WHO Region of the Americas recorded reductions in mortality in 2017 compared with 2010. The largest declines occurred in the WHO regions of South- East Asia (54%), Africa (40%) and the Eastern Mediterranean (10%). Despite these gains, the malaria mortality reduction rate has also slowed since 2015, reflecting the estimated trends in malaria case incidence (WHO 2018).

1.3 Economic Burden

The economic loss from malaria was estimated at US$2 billion in Africa alone in 1997. Malaria is a major cause of poverty, and poverty exacerbates the malaria situation. Taken together, the effects of malaria on lives and livelihoods are devastating for economic progress in hard-hit countries. The World Health Organization and the World Bank rank malaria as the largest single component of the disease burden in Africa, causing an annual loss of 35 million future life-years from disability and premature mortality. In Africa, malaria is responsible for about 20-30% of hospital admissions and about 30-50% of outpatient consultation. Malaria is also a major public health problem in parts of Asia, Latin America, the Middle East, and Eastern Europe. In India, epidemics of malaria are frequently reported from areas that previously were not associated with malaria (WHO, 2018).

Malaria limits international trade and development. The parts of the world that are continuously at high risk of malaria are predominantly the poorest (Alnwick, 2001). Malaria is the major cause of absenteeism from work and school in Africa and reduced productivity, reduction in labour supply, illness and death (Klausner and Alonso, 2004). Moreover, it is estimated that at least 1 million people die of malaria each year, mostly children under 5 years of age (WHO, 2005). More than 80% of the deaths worldwide occur in sub-Saharan African. (WHO 2005, Afolabi *et al*., 2001)

1.4 Economic Burden of Malaria in Nigeria

Nigeria's health care system as provided through the public sector is organized in a three tiered system. The federal government develops policies and guidelines, providing funding and technical support as well as monitoring and evaluating implementation, the 36 states provide the second tier of the system. The third tier is at the level of the local government. Although decentralization is a stated goal of the current health ministry, the states and the local governments primarily implement policies developed at the federal level (Carson *et al.,* 1998).

Local council health departments are required to establish educational malaria programme. With the prime focus being malaria control National Malaria Control Programme (2011). In Nigeria, there is an estimated 25%-30% of mortality in children under five or an estimated 300,000 deaths each year due to malaria.

April 2004 Nigeria's Health minister reported that it spent over $1 billion annually in treating malaria and that malaria was the cause of one out of three deaths in children and one out of ten deaths of pregnant women (English *et al.*, 2007). Chloroquine resistance was cited as a growing problem, owing in part to counterfeit drugs (Evans *et al.*, 2005) and (Ajayi *et al.*, 2003). Also, a director at the WHO disclosed that residents of Lagos State in Nigeria spend about N 1 trillion annually on malaria treatment.

More than 1 million children die annually from malaria in Africa (Allen *et al.*, 1996), a child dies every 30second from malaria in Africa,70% of deaths occur in children <5years of age (Cheesebrough, 2006). And even in the first 6 months of life (Afolabi *et al.*, 2001). Growing political commitment by African leaders for action on malaria was given a boost by the founding of the Roll Back Malaria (RBM) global partnership in 1998. Less than two years later African Heads of State and their representatives met in Abuja, Nigeria to translate RBM's goal of halving the malaria burden by 2010 into tangible political action. The Abuja Declaration endorsed RBM's goal and established a series of interim targets for the number of people having access to treatment, protective measures or, in the case of pregnant women, receiving intermittent preventive treatment to ensure that progress would be made towards the goal and malaria endemic countries and other RBM partners held responsible. Considerable progress has been made since Abuja. Almost 20 African countries have reduced or eliminated taxes and tariffs on insecticide-treated nets (ITNs) to make them more affordable. More than half the malaria-endemic African countries, representing almost half the population at risk have established Country Strategic Plans (CSPs) to achieve the RBM goal and the targets set in Abuja. CSPs are all based on the four technical elements of Roll Back Malaria and the evidence-based interventions associated with them prompt access to effective treatment promotion of ITNs and improved vector control, prevention and management of malaria in pregnancy and improving the prevention of, and response to, malaria epidemics and malaria in complex emergencies (Cheesbrough, 2006; Arora and Arora, 2008).

Countries are now working through local partnerships to develop the capacity to fully implement their CSPs using ongoing health sector reforms and linkages to other initiatives, such as Integrated Management of Childhood Illness (IMCI) and Making Pregnancy Safer (MPS) to improve access to key interventions. CSPs have been successful in attracting new resources for malaria control. However, given projected resource needs to the year 2010, only 20% of necessary funds will be available locally. African countries, working with their partners and donors, must identify and mobilize resources for the remainder. Countries are looking to a variety of sources to ensure sustainable financing of their efforts to Roll Back Malaria this includes traditional sources of funding, from the national treasury and donor community as well as the exploration of new opportunities through debt relief schemes and the newly formed Global Fund to Fight AIDS, TB and Malaria (WHO: Roll Back Malaria, 2000).

The ten highest burden countries in Africa reported increases in cases of malaria in 2017 compared with 2016. Of these, Nigeria, Madagascar and the Democratic Republic of the Congo had the highest estimated increases, all greater than half a million cases. In contrast, India reported 3 million fewer cases in the same period, a 24% decrease compared with 2016. Rwanda has noted a reduction in its malaria burden, with 430 000 fewer cases in 2017 than in 2016, and Ethiopia and Pakistan estimated decreases of more than 240 000 cases over the same period. The incidence rate of malaria declined globally between 2010 and 2017, from 72 to 59 cases per 1000 population at risk. Although this represents an 18% reduction over the period, the number of cases per 1000 population at risk has stood at 59 for the past 3 years (WHO 2018).

In 2017, an estimated US$ 3.1 billion was invested in malaria control and elimination efforts globally by governments of malaria endemic countries and international partners – an amount slighter higher than the figure reported for 2016. Nearly three quarters (US$ 2.2 billion) of investments in 2017 were spent in the WHO African Region, followed by the WHO regions of South-East Asia (US$ 300

million), the Americas (US$ 200 million), and the Eastern Mediterranean and the Western Pacific (US$ 100 million each). Also in 2017, US$ 1.4 billion was invested in low-income countries, US$ 1.2 billion in lower-middle income countries and US$ 300 million in upper-middle-income countries. International funding represented the major source of funding in low-income and lower-middle-income countries, at 87% and 70%, respectively (WHO 2018).

Governments of endemic countries contributed 28% of total funding (US$ 900 million) in 2017, a figure unchanged from 2016. Two thirds of domestically sourced funds were invested in malaria control activities carried out by national malaria programmes (NMPs), with the remaining share estimated as the cost of patient care. As in previous years, the United States of America (USA) was the largest international source of malaria financing, providing US$ 1.2 billion (39%) in 2017. Country members of the Development Assistance Committee together accounted for US$ 700 million (21%). The United Kingdom of Great Britain and Northern Ireland contributed around US$ 300 million (9%) while the Bill & Melinda Gates Foundation provided US$ 100 million (2%). Out of the US$ 3.1 billion invested in 2017, US$ 1.3 billion was channelled through the Global Fund to Fight AIDS, Tuberculosis and Malaria (WHO 2018). Although funding for malaria has remained relatively stable since 2010, the level of investment in 2017 is far from what is required to reach the first 2 milestones of the GTS; that is, a reduction of at least 40% in malaria case incidence and mortality rates globally by 2020, compared with 2015 levels. Stepping up investments in malaria research and development is a key to achieving the GTS targets. In 2016, US$ 588 million was spent in this area, representing 85% of the estimated annual need for research and development. Although research and development funding for malaria vaccines and drugs declined in 2016 compared with 2015, investments in vector control products almost doubled, from US$ 33 million to US$ 61 million (WHO 2018).

Presented in Table 1 below are facts and information on the economic burden and mortality rate in Africa and some of its countries within the space of ten (10) years, running into billions of US dollars and millions of death respectively.

Causative organism(s) of malaria

Malaria is caused by the protozoan parasite plasmodium. Human malaria is caused by four different species of plasmodium. *Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, and Plasmodium vivax.* Human occasionally become infected with plasmodium species that normally infect animal such as *plasmodium knowlesi.* As yet there are no reports of human mosquito human transmission of such "Zoonotic (Van Dooren and Striepen 2013).

2.1 Transmission

The malaria parasite is transmitted by female Anopheles mosquitoes, which bite mainly between dusk and dawn. It can also be transmitted through:

i. an organ transplant
ii. a transfusion

Plasmodium was first identified when Charles Louis Alphonse Laveran described parasites in the blood of malaria patients in 1880. He named the parasite ***Oscillaria malariae***. The fact that several species may be involved in causing different forms of malaria was first recognized by Camillo Golgi in 1886. Soon thereafter, Giovanni Batistia Grassi and Raimando Filetti named the parasites causing two different types of human malaria ***Plasmodium vivax*** and ***Plasmodium malariae*** (Hedrick, 2011). In 1897, William Welch identified and named ***Plasmodium falciparum.*** This was followed by the recognition of the other two species of plasmodium which infect human ***Plasmodium ovale*** and ***Plasmodium knowlesi*** (identified in long tailed macaques in 1931 in humans in 1965). The contribution of insect hosts to the plasmodium life cycle was described in 1897 by Ronald Ross and in 1899 by Giovanni Batista Grassi, Amico Bignami and Guiseppe Bastianelli (Hedrick, 2011).

Plasmodium is a genus of parasitic alvedates, many of which cause malaria in their hosts. The parasite always has two hosts in its life cycle: a dipeteran insect host and a vertebrate host. Sexual reproduction always occurs in the insects making it the definitive hosts (Van Dooren and Striepen 2013).

The life cycle of plasmodium species involve several different stages both in the insect and the vertebrate host. These stages include sporozoites which are injected by the insect vector into the vertebrate host blood. Sporozoites infect the host's liver giving rise to merozoites and (in some species) hypnozoites. These moves into the blood where they infect red blood cells, the parasites can either form more merozoites to infect more red blood cells or produce gametocytes which are taken up by insects which feed on the vertebrate hosts (Van Dooren and Striepen 2013).

In the insect host, gametocytes merge to sexually reproduce after sexual reproduction, parasites grows into new sporozoites, which move into the insects salivary glands, from which they can infect a vertebrate host bitten by the host. The genus plasmodium was first described in 1885, it now contains about 200 species which are spread across the world where both the insects and vertebrates hosts are present. Five species regularly infects humans, while many others infect birds, reptiles, rodents and various primates. Plasmiodium species each have 14 chromosomes in the nucleus as well as genetic materials in the mitochondrion and in the apicoplasts. The chromosomes vary from 500kilo-bases to 3.5megabases in length. The apicoplasts is involved in isoprenoid metabolism, Fe-S cluster synthesis, and fatty acid synthesis and phospholipids biosynthesis. On a molecular level, the parasites damages red blood cells using plasmepis enzymes aspartic acid proteases which degrades hemoglobin (Van Dooren and Striepen 2013).

2.2 Hosts

All plasmodium species are parasitic and require both a vertebrate host and an insect host to reproduce. Know vertebrate host include various primate (including humans), birds, rodents, bat, porcupines and squirrels. Mosquitoes of the genera culex, anopheles, culiseta, mansonia and aedes often serve as insect host for various plasmodium species (Van Dooren and Striepen, 2013).

2.3 Species That Infect Human

1. *Plasmodium falciparum;* the cause of malignant tertian malaria.
2. *Plasmodium vivax;* the most frequent cause of benign tertian malaria.
3. *Plasmodium malariae;* the cause of benign quartan malaria.
4. *Plasmodium ovale;* the other less frequent cause of benign tertian malaria.
5. *Plasmodium knowlesi;* the cause of severe quotidian malaria in South East Asia (Kwiatkowski, 2005).

Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae together account for nearly all human infection with plasmodium species, with *Plasmodium falciparum* accounting for the overwhelming majority of malaria deaths. An increasing number of cases of severe malaria in Southeast Asia have been attributed to *Plasmodium knowlesi* (Kwiatkowski, 2005). With the use of the polymerase chain reaction additional species have been identified in human although whether these species can regularly infect humans is not known (Gillian, 2006). Figure 1 illustrates the life cycle of malaria parasite both in the mosquito vector and human host.

2.4 Symptoms of malaria infection

The symptoms of malaria typically develops within 10days to 4weeks following infection. In some people symptoms may not develop for several months. Some malaria parasite can enter the body but will be dormant for long period of time. Common symptoms of malaria are; High fever, profuse sweating, headache, nausea, vomiting, diarrhea, anemia, muscle pain, convulsions, bloody stools, and coma (Grover *et al*., 2006).

Malaria can cause a number of life threatening complications, the following may occur;

i. Swelling of the blood vessels of the brain, or cerebral malaria
ii. An accumulation of fluid in the lungs that's cause breathing problems or pulmonary edema
iii. Organ failure of the kidneys, liver or spleen
iv. Anemia due to the destruction of red blood cells
v. Low blood sugar (Grover *et al*., 2006).

2.5 Treatments

Malaria can be treated using the following methods, though there's no vaccine available to prevent malaria;

1. *Using anti-malarial drugs*
2. *Keep a clean environment to avoid development of mosquitoes*
3. *Sleeping under* insecticide treated nets: is another method of control, a person sleeps under insecticide treated nets [ITNs]. The ITN works not only by creating a barrier between the mosquito and the intended meal, but also by killing the mosquito if it lands on the net, (Grover *et al.*, 2006).
4. *Covering your skin or using bug spray containing DEET (N,N-Diethyl –meta toluamide or diethyltoluamide) may also help to prevent infection.*
5. *Avoid stagnant water in the environment.*
6. Indoors Resident Spraying (IRS): One of the most effective methods of vector control is indoor residual spraying (IRS). In this method the inside wall of houses are sprayed with residual insecticides. When the mosquitoes rest on the wall, they absorb the insecticides through their feet (Alnwick 2001). The pesticides either kill them immediately or soon afterwards. Its cost, logistical complexity and moderate efficacy make it poorly suited for controlling malaria in rural areas of sub Saharan Africa.
7. Mosquito Modification: Other genetic approaches include modifying mosquitoes to produce offspring that cannot transmit disease but this failed because where several species of vector are present, a separate transgenic must be created for each one. (WHO, 2004, 2005).

3.0 Review of some antimalarial drugs

3.1 Drugs are substance used to treat an illness, relieve a symptom, or modify a chemical process in the body for specific purpose. Some antimalarial drugs were considered in this review which includes the following;

1. Chloroquine
2. Quinine sulfate(qualaquin)
3. Hydroxychloquine (plaquenil)
4. Mefloquine (lariam)
5. Combination of atovaquone and proguanil (malarone)
6. Artemether
7. Lumefantrine
8. Artemether and lumefantrine
9. Artesunate
10. Amodaquine
11. Amatem forte
12. Lonart
13. Lumapil
14. P-alaxine
15. Combantrine
16. Oraxyl.
17. Deoxcycline (doxy 100)
18. Clindamycin (cleocin)
19. Combasunate
20. Fansidar.

3.2 Classification of anti malarial drugs

Antimalarial drugs can be divided into three major classes based on;

1. Mechanism of action,
2. Therapeutic activity, and
3. Structure.

The first classification based on mechanism of action; based on this, five sub-classes of quinolines, artemisinins, antifolates, atovaquones and antibacterials are derived Table 2. Whereas, based on the therapeutic activity, five classes can also be obtained Table 3, which are; causal prophylaxis, suppressive prophylaxis, clinical cure, radical curatives and gametocidal. But the class based on the structure can be sub divided into ten (10) groups.

3.2.1 Classification based on structure

1) 4 aminoquinolines: (chloroquine, hydroxchloroqine, amodiaquine, pyronaridine)
2) 8 aminoquinolines: (primaquine, tafenoquine, bulaquine)
3) Cinchona alkaloids: (quinine, quinidine)
4) Quinoline methanol: (mefloquine)
5) Biguanides: (proquanil, chloroproguanil)
6) Diaminopyrimidines: (pyrimethamine)
7) Sulfonamides: (sulfadoxine, dapsone)

8) Tetracycline: (tetracycline, doxycycline)
9) Naphthoquinone: (atovaquone)
10) Sesquiterpene lactones; (artesunate, artemether, arteether)

3.3 Discussion on mechanism of action of the major classes

Quinolines

Quinoline has less affinity for heme, implying that mechanisms other than ion transport into the food vacuole and heme-drug interactions are required for the action of these drugs (Foley and Tilly, 1998). Quinine also interacts rather weakly with heme (Kd = 2.63 × 10-6 M) (Chou *et al.,* 1980), but has been shown to inhibit heme polymerization (Slater, 1993) and heme catalase activity (Ribeiro *et al*., 1997). In the absence of a specific transporter, quinine is likely to be accumulated less efficiently in the food vacuole (Ribeiro *et al*., 1997). This class is illustrated in Figure 2.

Artemisinin

Artemisinin and its derivatives are sequiterpene lactones. Once administered, the artemisinin derivatives are hydrolyzed rapidly to the biologically active metabolite dihydroartemisin. The mode of action of the artemisinin drugs has not been completely elucidated. The present knowledge is reviewed by (Meshnick *et al.,* 1996). The structure of artemisinin is unusual, and its activity is thought to depend on the presence of the endoperoxide bond, as molecules without it have no antimalarial activity (Brossi *et al*., 1988). The endoperoxide bond may interact with iron or heme, decomposing into free radicals (Meshnick *et al*., 1994, Paitayatat *et al*., 1997). Unlike many redox reactions, this process is not reversible, so a single drug molecule will produce only one free radical. The effect of free radicals on the malaria parasite is still not fully understood. Because the concentration of free radicals is insufficient to cause general membrane damage, one theory is that a "specific free radical target" exists. The artemisinin free radical can form a covalent bond with either heme or other parasite proteins (Yang *et al*., 1993, 1994) and an initial hypothesis was that a heme-artemisinin compound might inhibit the production of hemozoin. No evidence, however, of reduced quantities of hemozoin in artemisinin-treated *P. falciparum* cultures has been found (Asawamahasakda *et al*., 1994). Artemisinin also has been shown to bind to 6 specific *P. falciparum* proteins, one of which is a member of the translationally controlled tumor protein family but the precise effect of this protein alkylation on the parasite is still to be determined. This is demonstrated in Figure 3.

Antifolate

The antifolate drugs inhibit either dihydrofolate reductase (HFR) (pyrimethamine, cycloguanil) or dihydropteroate synthase (DHPS) (sulfadoxine). These are two key enzymes in de novo folate biosynthesis; inhibition of this metabolic pathway leads to the inhibition of the biosynthesis of pyrimidines, purines, and some amino acids. Antifolate antimalarial drugs interfere with folate metabolism, a pathway essential to malaria parasite survival (Asawamahasakda *et al*., 1994). This is demonstrated in Figure 4.

Atovaquone

It is generally agreed that atovaquone acts on the mitochondrial electron transfer chain, although more recently, its activity and synergy with proguanil has been ascribed to its interference with mitochondrial membrane potential. Atovaquone inhibits cytochrome c reductase activity in *P. falciparum* (Fry and Pudney, 1992). Atovaquone is a ubiquinone analogue that binds to the cytochrome bc1 complex of the parasite mitochondrial electron transport chain. The malaria mitochondria electron transport chain disposes of electrons generated by dihydroorotate dehydrogenase during the synthesis of pyrimidines (Gutteridge *et al*., 1979) and the inhibition of this process by atovaquone may kill the parasite (Hammond *et al*., 1985). More recently, it has been shown in *P. yoelli* that atovaquone also dissipates the mitochondrial membrane potential of the parasite which may kill the parasite by initiating a process similar to apoptosis. This is demonstrated in Figure 5.

Antibacterial

It is a bacterial protein synthesis inhibitor by inhibiting ribosomal translocation, in a similar way to macrolides. It does so by binding to the 50s rRNA of

the large bacterial ribosome subunit or by binding to the 30s ribosomal subunit of the parasite causing overlapping with the binding site of the oxazolidinone, pleuromutilin, and macrolide antibiotics, among others. It has bacteriostatic activity against a broad range of gram positive and gram negative bacteria (Abrahamsson *et al.,* 2012). This is demonstrated in Figure 6.
Table 4 however specifies the active component of the drugs; it also states the side and adverse effects of the drugs.

Conclusion
The adverse effect of antimalarial drugs has grown in the modern era; the number of toxic effects commonly attributed in the literature of malaria and particularly to less severe forms of the disease, has steadily decreased since the use of artemisinin combination therapy (ACT)

Recommendation

- Effective ways have to be developed to maintain the efficacy of the long lasting effects of artemisinin derivates.
- Malaria infection should be prevented at all cost by using the appropriate measures also drugs taken should only be prescribe by a doctor and the therapeutic dose should taken in order to prevent adverse effect that might lead to toxicity of the drugs used in case of over dose.
- Genetic modification of mosquitoes and the parasites should be improved upon in the malaria endemic areas.

Declaration of conflict of interest
The authors declare that there is no conflict of interest

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Table 1: Economic burden and mortality rate in Africa and some of its countries.

Countries	Year	Cost implication of treatment	Number of Death
Africa	1997	US $2 billion	35 million
Africa	2004	US $1 billion	1million death
Nigeria	2004	#1 trillion	< 500,000
Asia	2016	US $4.5 billion	3million
Nigeria	2017	US $3.1 billion	<300,000
Rwanda	2017	US $2.2 billion	<240,000
South East Asia	2017	US $300 billion	<200,000

TABLE 2: Classification based on mechanism of action

Class	Mechanism of Action
1. Quinolines (chloroquine, qualaquin, plaquenil)	• Inhibits heme crystallization required in the erythrocytic stage in the parasite
2. Artemisinins (artemether, artesunate, lumefantrine)	• Binds heme iron and/or iron and generates oxygen radicals. • Damages SERCA Ca^{++} P-ATPase in the parasite
3. Antifolates (lonart, amodaquine, lumapil)	• Inhibits DNA synthesis in the parasite
4. Atovaquones (malarone, combantrine, fansidar)	• Collapses mitochondrial membrane potential of the parasite
5. Antibacterias (oraxyl, doxy 100, cleocin)	• Ribosome inhibition in the parasite membrane • DNA gyrase inhibition-fluoroquinolones of the parasite

TABLE 3: Classification based on therapeutic activity

Class	Therapeutic activity
1. Causal prophylaxis (primaquine, proquanil)	• Destroys parasite in liver cells and prevent invasion of erythrocytes
2. Suppressive prophylaxis (chloroquine, mefloquine, doxycycline)	• Suppress the erythrocytic phase and thus attack of malarial fever can be used as prophylactis
3. Clinical cure (chloroquine, artemether, artesunate)	• Eradicate all forms of Plasmodium species from the body
4. Radical curatives (primaquine, p- alaxine,)	• Eradicate all forms of P. vivax and P.ovale from the body • Suppressive drugs + hypnozoitocidal drugs
5. Gametocidal (artemisinin, chloroqine, proquanil, pyrimethamine)	• Destroy gametocytes and prevent transmission • Prevents development of sporozoites

Table 4: Active component of the drugs, side and adverse effects

S/N	Drugs	Active component	Side effects	Adverse effects	Reference
1	Chloroquine	Chloroquine phosphate	headache, nausea,	vomiting blurred vision, itching, anorexia, diarrhea, aminotransferase elevations, abdominal- cramps	(Hedrick, 2011).
2	Qualaquin	Quinine sulfate USP	headache, nausea	cinchonism: vomiting, diarrhea, abdominal pain, hearing impairment, vasodilation, sweating, disturbance in cardiac rhythm	(Brian, 2008).
3	Plaquenil	Hydroxychloroquine sulfate	nausea, headache, loss of appetite, weakness	vomiting, weight loss, diarrhea, dizziness, blurred vision, mood change, hair loss, bleeding, confusion twitching, skin rash, spinning sensation, irritability	(Bateman, 1986).
4	Mefloquine (lariam)	Mefloquine hydrochloride	nausea, headache stomach upset, Fatigue, pain	vomiting, sleep disorder, skin rash, dizziness transient elevation of transaminases, leucopenia thrombocytopenia, decreased hematocrit	(Albay *et al.*, 2005).
5	Malarone	Atovaquone, proguanil hydrochloride, core,poloxamer 188	weakness, sweating headache,	pale skin, mood change, loss of balance light sensitivity, spinning sensation, diarrhea	(Albay *et al.*, 2005).
6	Artemether	Dihydroartemisinin, artemisinine lactol	Headache, joint pain, cough.	dizziness, loss of appetite, trouble sleeping chest pain, chills, tiredness,	(Schlagenhauf *et al.*, 2012).
7	Lumefantrine	Lumefantrine fluorenes	nausea, headache joint pain, cough	vomitimg, abdominal pain, irregular heartbeat loss of concentration	(Schlagenhauf *et al.*, 2012).
8	Artemether and Lumefantrine	Artemether, lumefantrine, organochlorides, β-artemether, chlorobenzene	weakness, fever	vasodilation, sweating, loss appetite, insomnia irregular heartbeat, vomiting, chest pain.	(Schlagenhauf *et al.*, 2012).
9	Artesunate	Dihydroartemisinin	cough, headache, loss of appetite	slow heartbeat, allergic reactions, dizziness abdominal pain, oral thrush, decrease in red blood cells, acute bronchitis, vomiting, skin disorder, yellowing of the eye.	(Hedrick, 2011).

10	Amodaquine	4 – aminoquinoline, diethyl amodiaquine	Headache, nausea, Joint pain,	dizziness, diarrhea, vomiting, skin rash abdominal pain, loss of appetite, difficult in Sleeping	(Albay *et al.,* 2005).
11	Amatem forte	Artemether,lumefantrine, dihydroartemisinin, dibutylamino	sweating, weakness	Increased appetite, anxiety, diarrhea, vomiting Mood change, difficult in sleeping, coughing Ringing in ears, irritability, abdominal pains	(Hedrick, 2011).
12	Lonart	Artemether, halofantrine, faritoporphyrin ix,	nausea, vomiting, Coughing	skin rash, trouble in sleeping, diarrhea, slight rise in transaminases and decrease in reticulocyte Count are transient, abdominal pain	(Hedrick, 2011).
13	Lumapil	Artemether, lumefantrine, lactose monohydrate	headache, weakness,	skin rash, diarrhea, weight loss, stomach pain, Difficulty in sleeping, spinning sensation	(Flach, 2007).
14	p-alaxine	Hydroartemisinin, piperaquine	headache, back pain muscle pain, cough	loss of appetite, sweating, anxiety, dizziness swelling of limbs, confusion, abdominal pains	(Flach, 2007).
15	Combantrine	Mebendazole, arylaminoalcohol	headache, weakness loss of appetite, fever	cold, sore throat, convulsion, skin rash abnormal movement of the tongue, joint pains back pain, stomach upset, sweating.	(Albay *et al.,* 2005).
16	Oraxyl	Oxytetracycline, aztreonam, azlocillin, atenolol.	weakness, mild Diarrhea, headache Nausea, vomiting	skin rash, vaginal itching or discharge, dizziness loss of appetite, sweating, anxiety, upset stomach	(Abrahamsson *et al.*, 2012).
17	Cleocin	Clindamycin hydrochloride, lincomycin	headache, weakness	skin reaction, abdominal pain, vaginal itching Sore throat, short breath, difficult in sleeping	(Abrahamsson *et al.*, 2012).
18	Combasunate	Artemether, lumefantrine, chlorobenzene, methyl ether	headache, weakness back pain, loss of appetite.	vasodilation and sweating, dizziness, cough, vomiting, chest pain, mood change, joint pains difficult in sleeping	(Flach, 2007).
19	Fansidar	Sulfadoxine, pyrimethamine	headache, muscle weakness, felling full, stomach pain coughing, joint pain.	hair loss, depression, nervousness, diarrhea dizziness, vomiting, pale skin, hallucination sore throat, short breath, loss of appetite.	(Zimmerman, 2013).

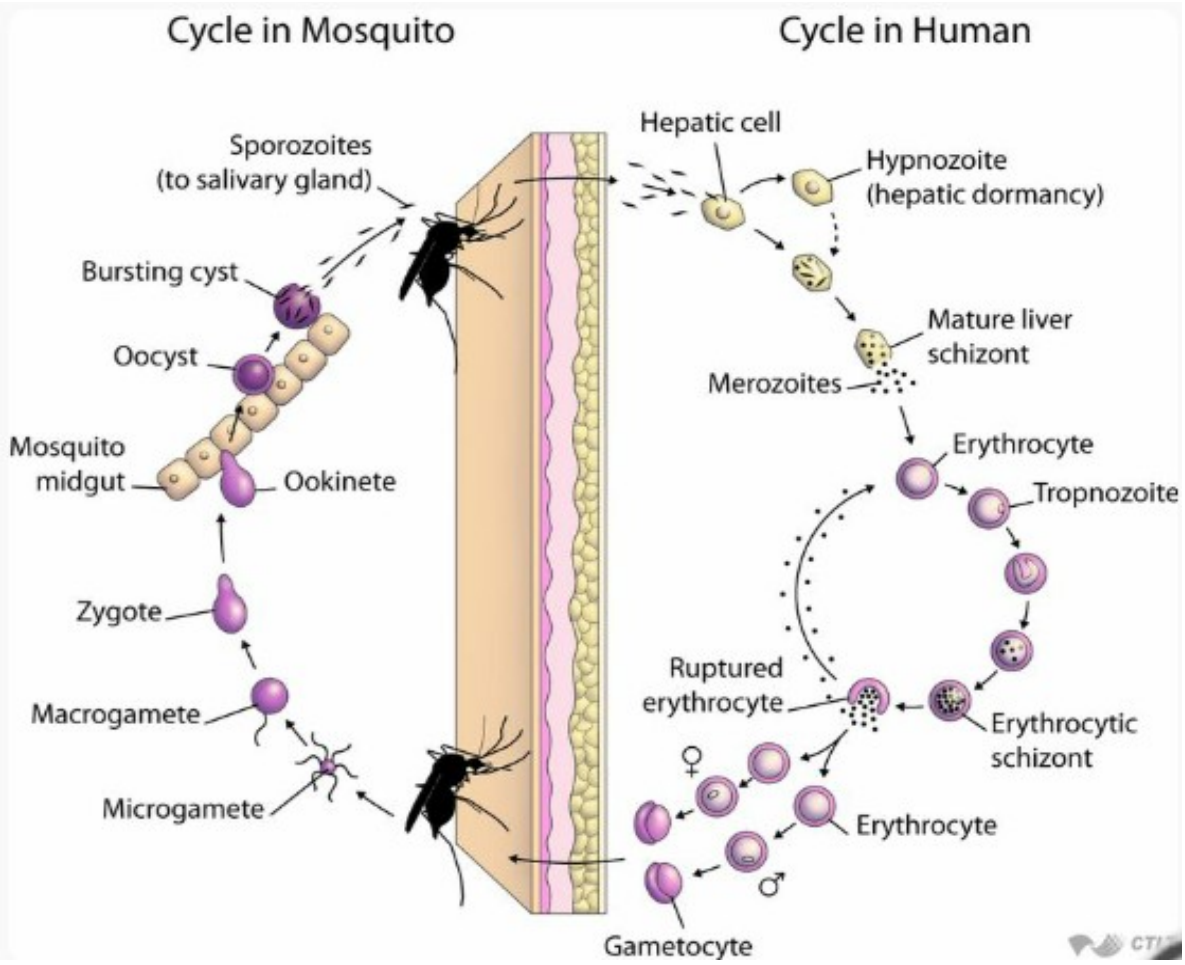

Figure 1: Life cycle of malaria parasite
(Grover *et al.*, 2006)

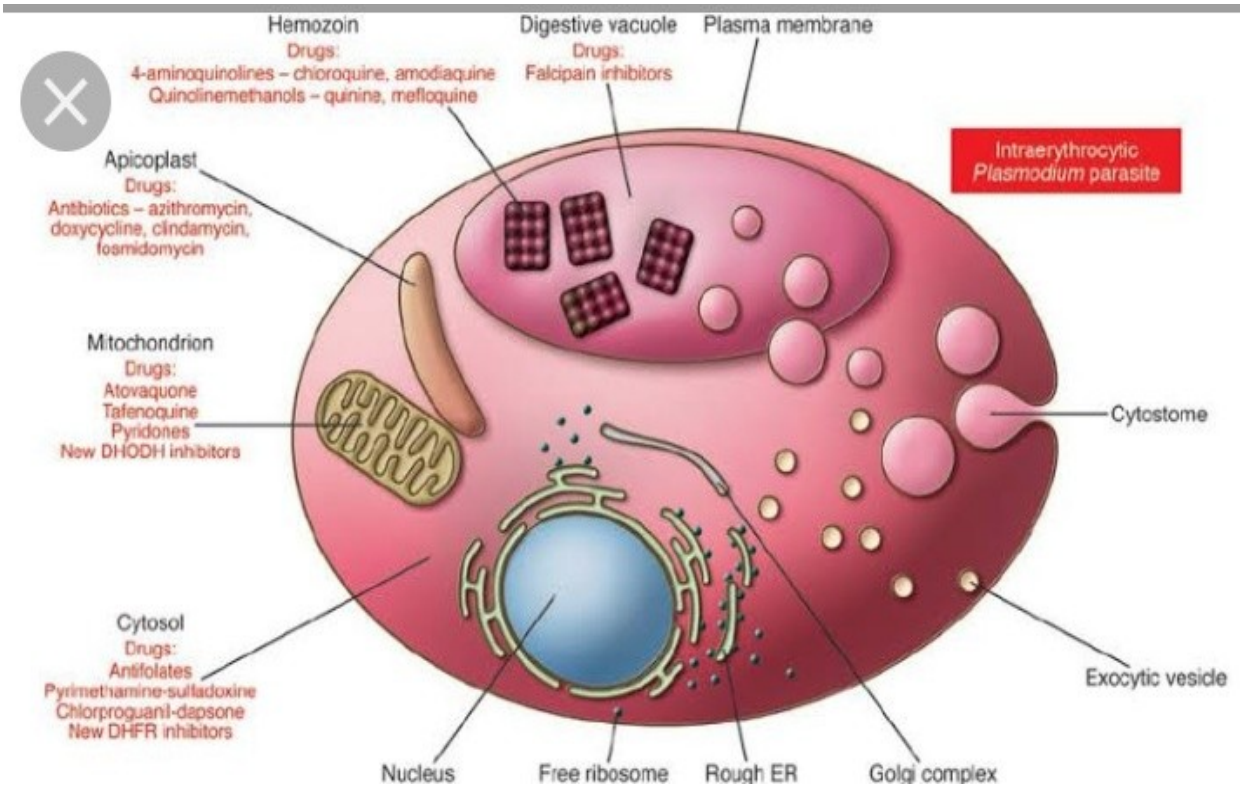

Figure 2 (Ribeiro *et al.*, 1997)

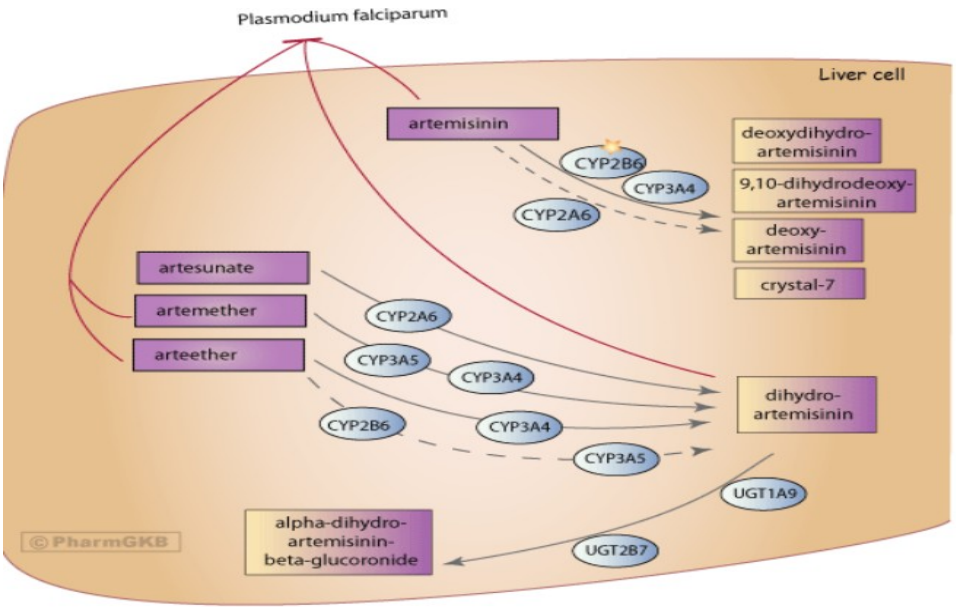

Figure 3 (Asawamahasakda *et al*., 1994)

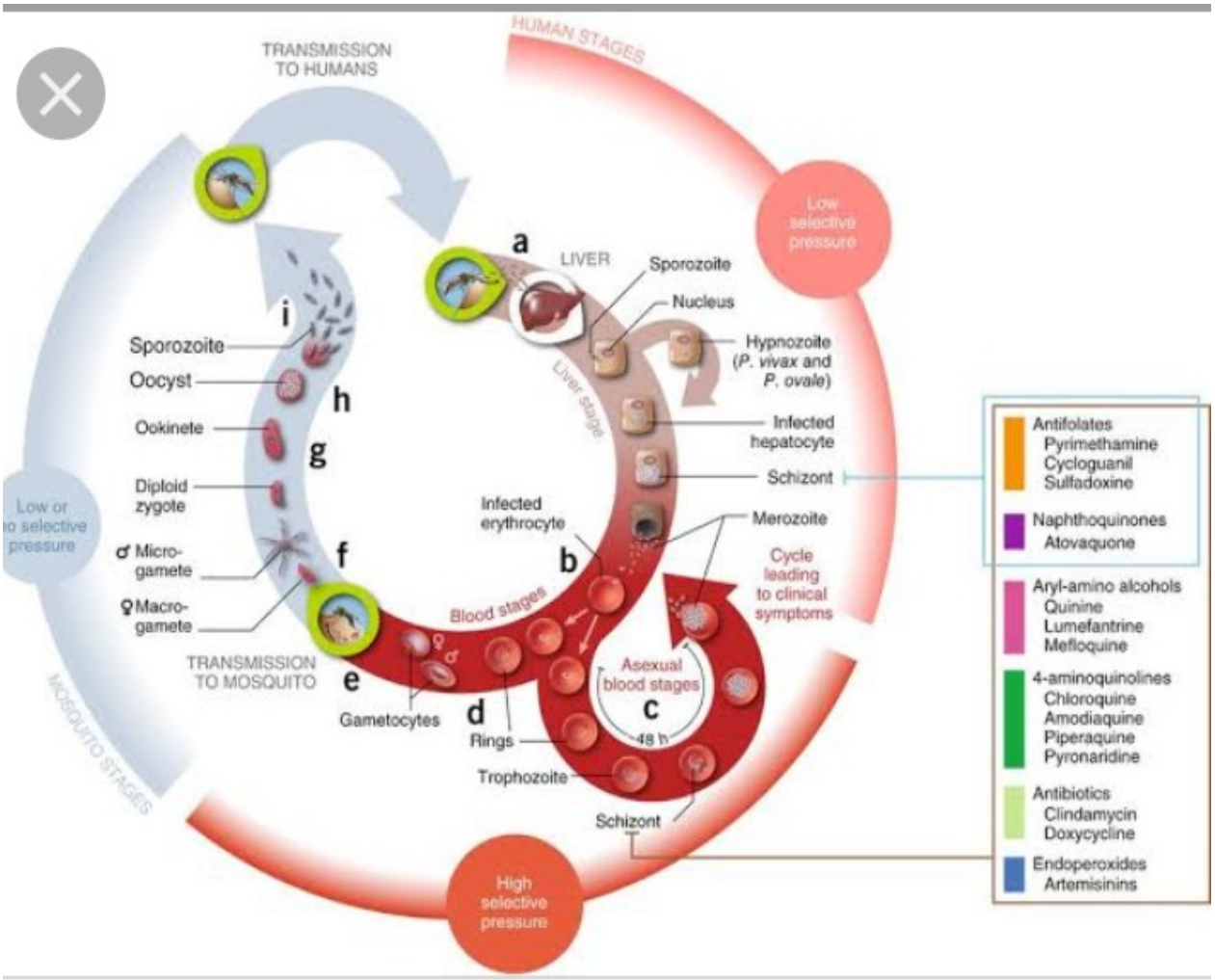

Figure 4 (Asawamahasakda *et al.*, 1994)

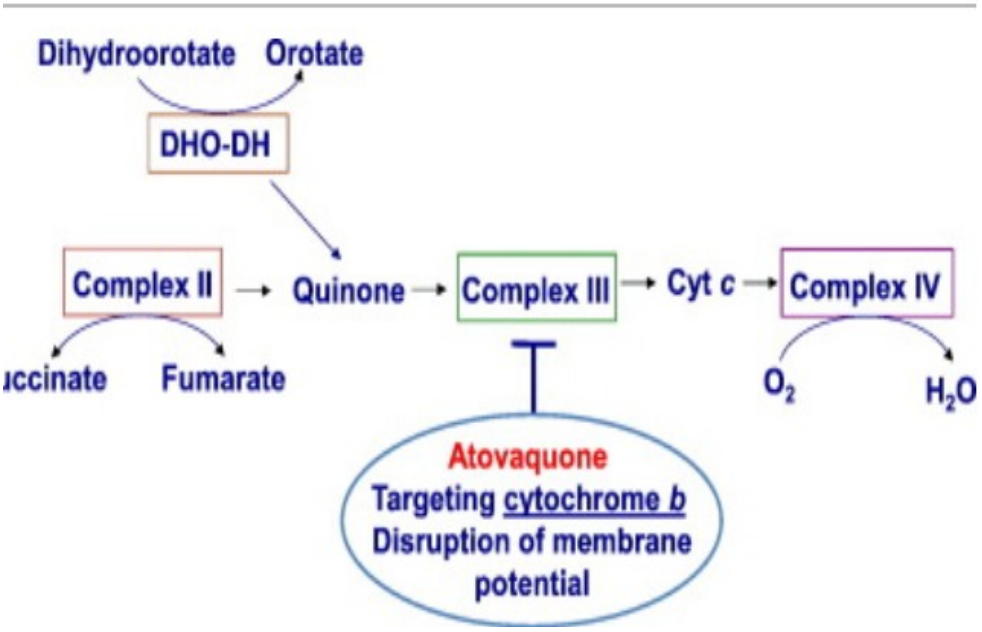

Figure 5 (Hammond *et al.*, 1985)

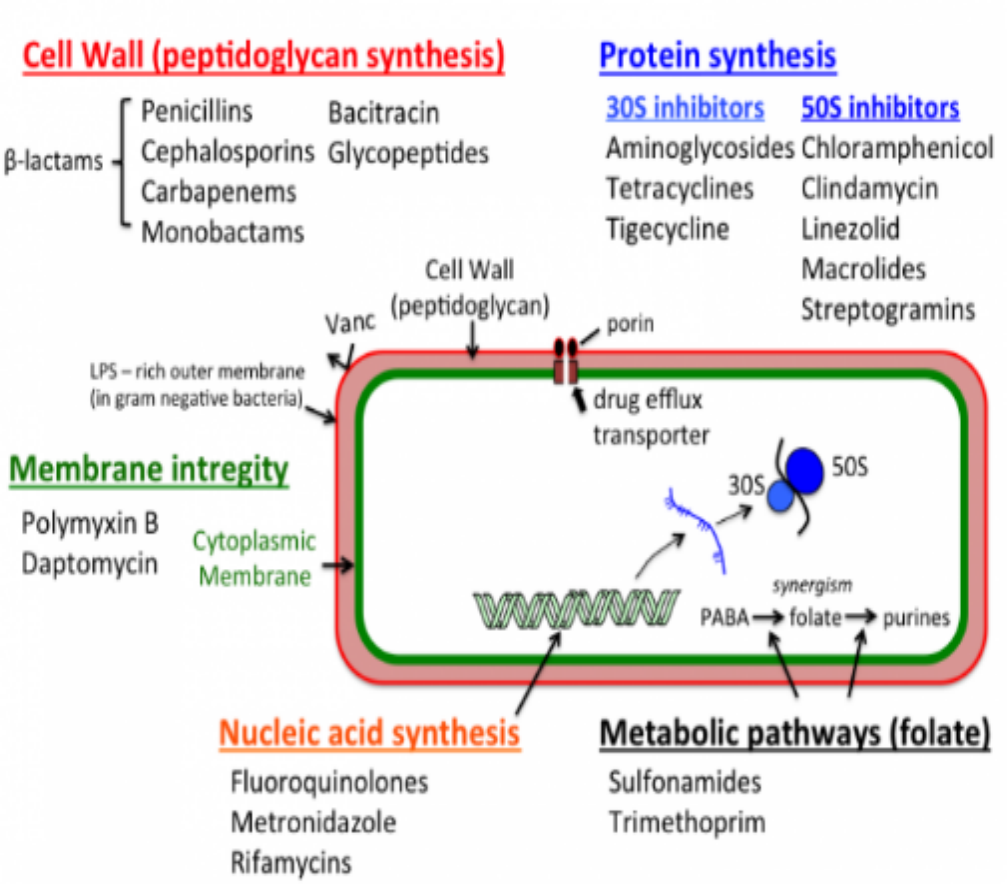

Figure 6 (Abrahamsson *et al.*, 2012)