Review Article

A Coherent Study on Various Strategies to Combat Malaria

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Abstract

Despite extensive research and various control programs, malaria is still a major global public health threat. It is responsible for approximately 300–500 million clinical cases and 1.2 million deaths annually. To decrease the menace of malaria, it is imperative to regulate the spreading of this formidable disease. This can be accomplished by control of Anopheles mosquito vector by insecticides, reduction of human-vector contact, and prevention and treatment of the disease with antimalarial drugs. New technical approaches are needed to identify novel drug candidates, so that adequate and effective antimalarial drugs can be made available clinically. Besides, a multivalent vaccine that can be effective against multiple stages of the parasite is urgently needed to achieve the goal of complete malaria eradication.

Keywords: Malaria, Plasmodium, Anopheles, Antimalarial drugs, vaccines.

Introduction

Malaria influences largely the economies and development of the nations for millennia. It has been reported to be responsible for crushing defeats during wars as sometimes more soldiers were killed by malaria than battle. It was first thought to be caused by poisonous vapours from standing water or swamps and therefore the Italians called the disease “mala–aria”, which means “bad air”. The joining of two terms is known as “malaria”, which is a misnomer but still used today to describe the disease.

Malaria is caused by an apicomplexan protozoan parasite of genus Plasmodium and spread by the female Anopheles mosquitoes. Mainly four species of parasite are reported to infect humans naturally: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae. Plasmodium knowlesi, a nonhuman primate malaria parasite, has recently been identified as being responsible for a significant number of human cases in South-East Asia [1]. Among these species, P. falciparum causes the most severe form of disease and is responsible for almost all malaria mortality. However, in tropical and subtropical areas, P. vivax can equal P. falciparum as a source of malaria morbidity and is the most widespread species outside Africa [2] in South America and Asia, while infections with P. malariae and P. ovale subspecies are usually mild [3].

Historically malaria occurred in many parts of the world but mortalities steadily decreased from 1900 to 1997 all over the world, except in sub-Saharan Africa, where, there was significant increase in mortalities [4, 5]. Malaria has persisted through the development of miracle drugs and insecticides, a global eradication effort, and so many years of intensive efforts to develop a practical vaccine. Still, it is one of the most prevalent parasitic diseases responsible for nearly 250 million new clinical cases annually resulting in about 1.2 million deaths, the majority of children in sub-
Saharan Africa [6]. However, as a result of a massive scale-up in malaria control programs by the WHO as part of the Millennium Development Goals, the estimated incidence of malaria globally has reduced by 17% and malaria-specific mortality rates by 26% between 2000 and 2010 [7]. Although, it represents some progress in reducing the disease burden, however malaria still remains a major global health threat and continues to cause high morbidity and mortality, especially in sub-Saharan Africa, where almost 600 million people are at risk [8].

**Malaria control strategies**

**Vector Control**

Various chemical, physical and biological measures have been employed to control the vector. Chemical control involves use of insecticides such as organophosphates, chlorinated hydrocarbons like dieldrin, benzene hexachloride (BHC) and synthetic pyrenoïds such as deltamethrin, cyfluthrin etc. Indoor residual spray (IRS) with insecticides continues to be the mainstay for malaria control. It affects the malaria transmission by reducing the life span of female mosquitoes thereby reducing the density of the mosquitoes [9]. Fogging is the process of using of a pesticide, such as natural pyrethrum extract, synthetic pyrethroid and malathion, it is used in the form of very fine droplets that resemble smoke or fog. Insecticide-treated nets (ITNs), infused with pyrethroids, not only decline the contact with mosquitoes but also destroy the mosquito with its residual insecticidal action [10].

Biological control involves the use of various biological agents to control the vector population. Two bacterial species, Bacillus thuringiensis israelensis and Bacillus sphaericus, have been widely demonstrated to be effective larvicides against mosquitoes [11]. Several larvivorous fishes like Poecilia eticulate (Guppy) and Gambusia affinis have been used for biological control of mosquito population. In another approach, symbiotic bacteria were used to deliver antimalarial molecules to the mosquito midgut to provide resistance against malaria. The Escherichia coli hemolysin A secretion system was used to stimulate the production of various anti-Plasmodium effector proteins by Pantoea agglomerans, a common mosquito symbiotic bacterium. These engineered *P. agglomerans* strains inhibited development of the *P. falciparum* and *P. berghei* by up to 98%. Significantly, the proportion of mosquitoes carrying parasites decreased by up to 84% for two of the effector molecules, scorpion, a potent anti-plasmodial peptide and four copies of *Plasmodium* enolase-plasminogen interaction peptide (EIP) that prevents plasminogen binding to the ookinete surface. These results provide the basis for the use of genetically modified symbiotic bacteria to fight malaria [12].

Studies on the efficacy of natural plant products as larvicides have indicated them as an alternative to synthetic chemical insecticides. Importance of various plants such as Solanum nigrum [13], Hibiscus abelmoschus [14], Spilanthes acmella Murr. [15], Carica papaya [16] and neem [17] have been experimentally proved. Sterile insect technique is emerging as a potential method to control malaria vector. Progress towards transgenic or genetically modified insects suggests that wild mosquito populations could be made malaria resistant. The technology has allowed the production of the genetically modified vectors that are either resistant/refractory to the parasite infection or decreased life span of the vector mosquitoes [18]. Individual protection from mosquitoes can be achieved through a number of methods, including mosquito repellents, protective clothing, insect screens, and residual treatment of interior walls with insecticides can be employed to control malaria vector [10].

**Chemotherapy**

New technologies and high throughput approaches are identifying a number of drug candidates, however only a limited number of antimalarial drugs have emerged from the development pipeline to enter clinical practice over the past century [19].

**Quinine and its derivatives**

Quinine, the first pharmaceutical agent used to treat malaria, was derived from the bark of Cinchona calisaya [20]. The 4-aminoquinoline derivatives of quinine include chloroquine, aminophenols, amodiaquine, pyronaridine, and piperaquine. The 8-aminoquinolines include the prototype pamaquine, primaquine and tafenoquine (anti-hypnozoite form treatment). Other derivatives of quinine include the arylamino alcohols mefloquine, halofantrine, and lumefantrine [21]. Both chloroquine and primaquine are still in use today and probably act by interfering with the parasite’s ability to eliminate the toxic by-products of hemoglobin digestion. The development of resistance by *Plasmodium* to conventional anti-malarial drugs, such as chloroquine and amodiaquine, has posed a tough challenge to control measures. Chloroquine resistance by *P. falciparum* reached East Africa from the East in 1978 and had crossed the African continent by 1985 [22]. Chloroquine resistance has also been observed in *P. vivax* [23].
Antifolates

These drugs have specific enzyme targets in the parasite and inhibit the parasite’s essential ability to synthesize tetrahydrofolate used for methylation reactions [24]. Sulfadoxine-pyrimethamine became available in 1971 as second-line therapy for malaria [25]. Indeed, resistance to antifolate drugs evolved more rapidly than resistance to chloroquine [24].

Artemisinin combination therapy

Artemisinin, an active ingredient of Artemisia annua, a Chinese herb (Quinghaosu) was isolated in 1972. Various synthetic oils and water-soluble derivatives of artemisinin include dihydroartemisinin (DHA), artemether, arteether, artesunate and artelinic acid. Artesunate, artemether and arteether are the fastest acting anti-malarials [26]. The artemisinin derivatives are also active against the sexual forms (gametocytes) of the parasite and can therefore reduce transmission rates [27]. Constant use of artemisinin monotherapy resulted in artemisinin-resistant parasites in the Cambodia-Thailand border region, a historical epicenter for the development and spread of antimalarial drug resistance [28]. In response to this, the WHO recommended artemisinin-based combination therapy (ACT) as first-line treatment for falciparum malaria. ACT is the combination of artemisinin or an artemisinin derivative (e.g., artesunate, artemether, dihydroartemisinin) and a partner drug (e.g., amodiaquine, mefloquine, piperaquine, lumefantrine) having a markedly longer half-life in the bloodstream than artemisinin. The five ACTs currently recommended for use are artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine (SP), and dihydroartemisinin plus piperaquine. The choice of the ACT should be based on the efficacy of the combination in the country or area of intended use [29].

The success of artemisinin combination therapy in recent years has prompted discussions of malaria elimination or eradication in the near future [30]; however, measures to prevent or impede the appearance of drug-resistant parasites should be considered for such a large-scale use of artemisinin to eliminate malaria parasites in endemic regions because delayed parasite clearance after treatment of artemisinin derivative has been reported [31]. Reduced sensitivity to artemisinins in turn renders the ACT partner drugs more vulnerable to the development of resistance. In response to this alarming pattern, WHO (2011) [29] has formulated a ‘Global Plan for Artemisinin Resistance Containment (GPARC)’ to address the need for specific and immediate actions to limit spread. Several candidate genes have been proposed to be important in the development of artemisinin resistance [32], but this remains a key ongoing area of research. Recently, the putative gene of P. ovale dihydrofolate reductase-thymidylate synthase (PoDHFR-TS), a known antifolate target, has been identified and sequenced [33]. PoDHFR from Thai isolate EU266602 remains sensitive to the antimalarials pyrimethamine and cycloguaniil, in contrast to P. falciparum and P. vivax isolates, where resistance to these drugs is widespread [34].

New drug candidates

Pyronaridine, a 4-aminoquinoline, is being used in combination with artesunate as a promising new artemisinin-based combination therapy. Pyronaridine-artesunate has been studied in phase II and phase III clinical trials, and has been shown to be effective against uncomplicated P. falciparum and blood stage P. vivax [35]. Tafenoquine, an 8-aminoquinoline, is a lead candidate drug aimed as a radical cure of P. vivax for elimination of dormant hypnozoites, and is being studied in a phase II/III tafenoquine/chloroquine combination study. A fixed dose artemisinin combination therapy, artesunate-amodiaquine (Coarsucam/ASAQ, Winthrop) has been approved by WHO and is undergoing phase IV field assessment [19].

‘Rational design approach’ resulted in the identification of a new candidate antimalarial, the spiroindolone NITD609, in which molecules are selected from existing chemical data, and hits (molecules) are recognized through high throughput screening with whole parasites. This compound has been found to be safe for humans [19]. Mass screening of chemical libraries has yielded a wealth of potential antimalarial compounds. Screening of 2816 registered or approved compounds led to 32 compounds, which were found to be active against 45 parasite lines sourced from different parts of the world with IC50 values ≤1 mM, including 10 compounds not previously known to have anti-malarial activity [36]. The endoperoxide feature of artemisinins is shared by ozonide OZ439, a synthetic endoperoxide. OZ439 is currently undergoing phase II trials and carries the hope of providing a single dose oral cure in humans when used in combination. It is highly effective drug against asexual stages of Plasmodium and will likely be developed for use in combination with a partner drug with a longer half-life than its own [37].

Vaccines

Vaccines could be a crucial component of efforts to eradicate malaria. Malaria vaccines are generally divided
into three groups based on stages of the parasite life cycle that are targeted: pre-erythrocytic, asexual blood-stage, and transmission-blocking vaccines.

**Pre-erythrocytic vaccines**

Pre-erythrocytic vaccines prevent entry of sporozoites into hepatocytes and therefore inhibit their development into tissue schizonts. Vaccination with radiation-attenuated sporozoites formed the starting point for the extensive investigations into pre-erythrocytic vaccines. Synthetic and genetically engineered sub-unit vaccines have generally been based on the two surface proteins, circumsporozoite protein (CSP) and thrombospondin related anonymous protein (TRAP) involved in sporozoite motility and invasion of liver cells [38].

Some of the identified liver stage antigens include LSA-1, LSA-2 and LSA-3. PiLSA-3 DNA immunization induced potent Th1 response with protective properties and conferred protection against *P. yoelli* challenge in mice [39]. Immunization with PfCeTOS resulted in potent humoral and cellular immune responses and most importantly induced sterile protection against a heterologous challenge with *P. berghei* sporozoites. CeTOS-specific antibodies resulted impairment of sporozoite motility and hepatocyte infectivity. The results underscore the potential of this antigen as a pre-erythrocytic vaccine candidate and demonstrate for the first time a malaria vaccine that is cross protective between species [40]. RTSS/AS01, also known as mosquirix, was recently evaluated in a phase 3 trial in seven African countries. It reduced malaria burden by half in children aged 5 to 17 months during one year follow up after vaccination [41].

**Asexual blood stage vaccines**

Vaccines based on asexual blood-stage antigens may be effective at reducing parasite densities and provide protection against clinical disease. Although a number of blood-stage vaccines have been developed and tested in preclinical and clinical trials, only limited clinical success has been achieved with blood-stage vaccines to date [42]. Blood stage malaria vaccines have been developed based on a few number of parasite antigens namely the Merozoite Surface Proteins (MSPs), Apical Membrane Antigen-1 (AMA-1) and Erythrocyte Binding Antigen-175 (EBA-175) [43]. A three-component blood-stage malaria vaccine consisting of recombinant *P. falciparum* blood stage proteins MSP1, MSP2 and RESA (Combination B) has been evaluated in a Phase I-II b trial and was found to be safe and immunogenic in adults and children (5–9 years) [44]. Vaccination with recombinant AMA1 has been shown to elicit antibody responses that provide protection against homologous parasite challenge in a number of rodent and primate models. AMA1-C1/ISA 720 vaccine was found to be immunogenic and the level of antibody response and biologic activity was comparable to other formulations of adjuvanted AMA1-C1 [45].

Serine repeat antigen (SERA) of *P. falciparum* has been reported to induce parasite inhibitory antibodies [46], and protective immune response in Panamanian *Aotus* monkeys [47]. Dodoo et al. [48] reported that the glutamate-rich protein (GLURP) of *P. falciparum* is a candidate for a malaria vaccine component because the levels of anti-GLURP IgG antibodies correlate significantly with protection from clinical malaria. PyTRAMP, a merozoite surface protein, has high degree of conservation when compared with homologous proteins from other *Plasmodium* species. The broad recognition by sera from *P. vivax*-infected people support further studies aimed at evaluating its immunogenicity and protective ability (as a full protein or its derived synthetic peptides) in a relevant biological model, such as the *Aotus* monkey [49]. A recombinant malaria vaccine based on receptor binding domain of *P. falciparum* EBA-175 (referred to as PfF2) formulated with human compatible adjuvants, Montanide ISA720, ASO2A and alum was found to be immunogenic and was able to induce invasion inhibitory antibodies [50]. Erythrocyte-binding antigens (EBAs) are important erythrocyte invasion ligands used by merozoites and may be targets of protective immunity in humans and these can be evaluated as potential vaccine candidates [51].

**Transmission-blocking vaccines**

Transmission-blocking vaccines (TBVs) are aimed at blocking malaria transmission by interrupting the parasite life cycle in the mosquito. TBVs as such do not directly protect vaccinated individuals from infection; however, they could contribute to elimination of the disease by lowering the parasite transmission efficiency. The leading candidate vaccines contain the *P. falciparum* ookinet surface antigens Pf25 and Pf30 or their *P. vivax* homologues Pvs25 and Pvs28 [52]. Transmission of the transgenic *P. berghei* expressing the P25 antigens of either *P. falciparum* or *P. vivax* was blocked by antibodies, obtained from animal vaccination and phase I clinical trials. Other antigens that are being developed as transmission-blocking vaccines are gamete antigens Pf1843/45 and Pf1230 [53].
Summary

From above discussion, it can be concluded that the future of malaria control requires the availability of effective and inexpensive drugs, an effective vaccine and control on Anopheles vector population. A highly efficient vaccine having impact on transmission of all life stages needs to have antigens from pre-erythrocytic, erythrocytic, sexual or mosquito stages into a single target multi-component vaccine. Moreover, search for novel antimalarial compounds, and identification of new drug targets is the need of hour. Health awareness among people and amplification of health policies in endemic areas is needed to combat this dreadful disease.

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Conflict of Interest

Authors hereby declare that there is no conflict of interest.

References


