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EMERGING TRENDS IN THE MANAGEMENT OF MALARIA

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ABSTRACT

Malaria has remained a major cause of morbidity and mortality in the under developed and developing countries of the tropical and sub-tropical regions of the world. Although effective ways to manage malaria now exist, the number of malaria cases is still increasing, due to several factors. A multitude of novel malaria vector-control tools has been developed in recent years, and several of these are at an advanced stage, nearing broad-scale implementation. Researchers have created a credit-card sized tool (malaria test card) to test for malaria. Parasite resistance to almost all commonly used anti-malarials has been observed in the most lethal parasite species, *Plasmodium falciparum*. This has presented a major barrier to successful disease management in malaria-endemic areas. At present, Artemisinin-based combination therapy (ACT), are recommended for treatment of resistant *P. falciparum* infections. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria. This article addresses the latest research and developments on the management of malaria like new technologies in the prevention, diagnosis, therapy of malaria and vaccines.

KEYWORDS: Malaria, prevention, diagnosis, antimalarial drugs, vaccines.

INTRODUCTION

Malaria is a protozoa disease, transmitted by the Anopheles species of mosquito carrying the *Plasmodium* parasite. Species of the genus *Plasmodium* including *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* are known to cause malarial infections in humans, virtually all deaths are caused by *P. falciparum.*[1] Occasionally malaria is transmitted by blood transfusion or congenitally from mother to fetus. The disease is characterized by fever and influenza-like symptoms, which may occur at intervals and which include chills, headache, myalgia, and malaise. Malaria may be associated with anaemia and jaundice, and *P. falciparum* infections may cause kidney failure, coma, and death.[2] Malaria is not just a disease commonly associated with poverty, but is also a cause of poverty and a major hindrance to economic development. The economic impact of malaria has been estimated to cost Africa $12 billion every year. The economic impact includes costs of health care, working days lost due to sickness, days lost in education.[3] The development and spread of parasite resistance to certain anti-malarial agents has presented a major barrier to successful disease management in malaria-endemic areas, and has probably contributed to the resurgence of infection and the increase in malaria-related deaths in recent years.[4] In this review an update of malaria prevention, diagnosis and therapy is presented and discussed highlighting the recent advances in the management of malaria.

Spread of malaria

Malaria, a parasitic disease spread to humans by mosquitoes, is common in warm climates of Africa, South America and South Asia. The development and survival, both of the mosquito and the malaria parasite are highly sensitive to daily and seasonal temperature patterns and the disease has traditionally been rare in the cooler highland areas.[5] Presently researchers had found that climate changes and other factors interact to play a role in the spread of malaria. For examples, people migrating from lowlands may be introducing the malaria parasite into highland regions, changes in farming practices may also play a role and irrigation associated with more intensive farming may be creating more places for mosquitoes to breed.[6] Over the last 40 years, however, the disease has been spreading to the highlands, and many studies link the spread to global warming. Due to global warming, the number of geographic area inflicted with malaria is increasing, causing multiple malaria endemics. Global climate change due to human action is now a scientifically proven fact and many developing countries would bear the brunt of all possible outcomes. However, despite being the most serious consequence, health has received inadequate attention in the larger policy dimension.[7]

Malaria prevention

Malaria prevention consists of a combination of mosquito avoidance measures and chemoprophylaxis. Although very efficacious, none of the recommended interventions are 100% effective. Five proven

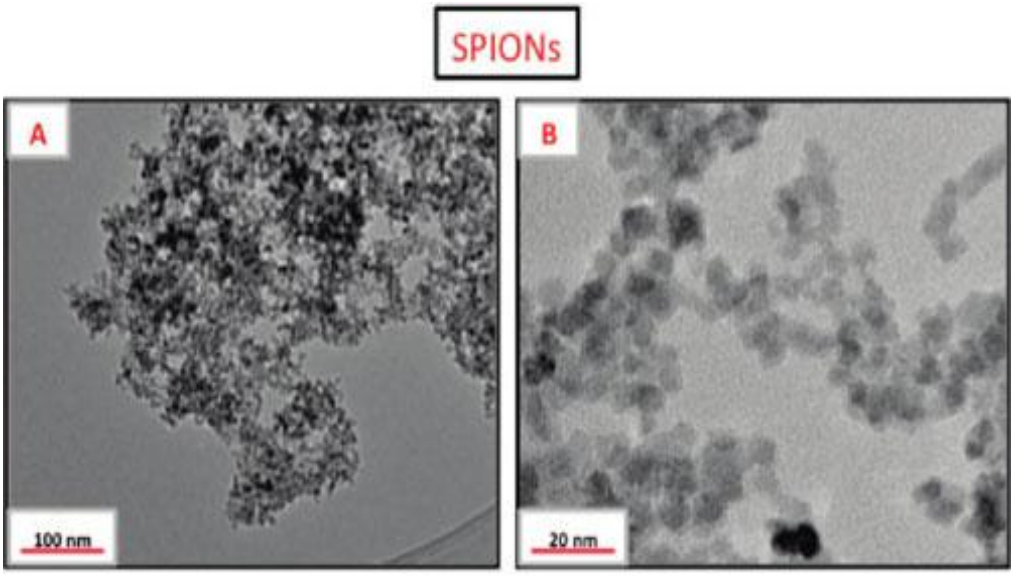
interventions currently are long-lasting insecticide-treated mosquito nets (ITNs)[8], indoor residual spraying (IRS)[9], improved diagnosis using rapid diagnostic tests (RDTs)[10], the use of artemisinin combination therapy (ACT) as first-line therapy[11] and protection of women with intermittent preventive treatment during pregnancy (IPTp).[12] Prevention through widespread use of ITNs or IRS, for example, might reduce the level of malaria transmission to the point that pregnant women are no longer at measureable risk of asymptomatic malaria, suggesting that IPTp interventions may no longer be needed.[13] IRS and ITN effectiveness is threatened by the emergence of insecticide resistance . Novel applications of IRS using rotational (alternating insecticides over time) or mosaic (multiple insecticides in different areas) strategies might preserve the effectiveness of this intervention.[14]

Recently, a multitude of novel malaria vector-control tools has been developed. Successes were reported in Kenya with *Bacillus thuringiensis israelensis* (Bti) for larval control.[15] Novel tools for the control of the adult mosquito include entomopathogenic fungi, insect-pathogenic viruses, the introduction of genetically engineered mosquitoes and the sterile insect technique (SIT).[16, 17] Field-based trials in which the impact of these vector-control tools on public health is properly measured are needed before they can be adopted to complement the malaria control tools currently in use.[18]

Several drugs, most of which are also used for treatment of malaria, can be taken preventively. Generally, these drugs are taken daily or weekly, at a lower dose than would be used for treatment of a person who had actually contracted the disease.[19] Use of prophylactic drugs is seldom practical for full-time residents of malaria-endemic areas, and their use is usually restricted to short-term visitors and travelers to malarial regions. This is due to the cost of purchasing the drugs, negative side effects from long-term use, and because some effective anti-malarial drugs are difficult to obtain outside of wealthy nations.[19] Modern drugs used preventively include *mefloquine* (Lariam), *doxycycline* (available generically), and the combination of *atovaquone* and *proguanil hydrochloride* (Malarone). The choice of which drug to use depends on which drugs the parasites in the area are resistant to, as well as side-effects and other considerations.[20]

Preventing the foci of resistant falciparum malaria from widening requires the rational use of antimalarials and the intensification of vector control, such as source reduction through destruction of mosquito breeding sites, and avoidance of man-vector contact by using protective measures, e.g., bed nets and repellents. These measures call for combined individual and community participation, and can be used in developing broader-based control strategies.[21]

Vaccines for malaria are under development, with no completely effective vaccine yet available. Presently, there is a huge variety of vaccine candidates on the table. Pre-erythrocytic vaccines (vaccines that target the parasite before it reaches the blood), in particular vaccines based on circumsporozoite protein (CSP) [22], make up the largest group of research for the malaria vaccine. Other vaccine candidates include: those that seek to induce immunity to the blood stages of the infection; those that seek to avoid more severe pathologies of malaria by preventing adherence of the parasite to blood venules and placenta; and transmission-blocking vaccines that would stop the development of the parasite in the mosquito right after the mosquito has taken a bloodmeal from an infected person. It is hoped that the sequencing of the *P. falciparum genome* will provide targets for new drugs or vaccines.[23]The next generation of malaria vaccine is to be delivered through nanoparticles. Researchers had demonstrated the use of magnetofection for the delivery of malaria DNA vaccine[24] as shown in Fig 1.



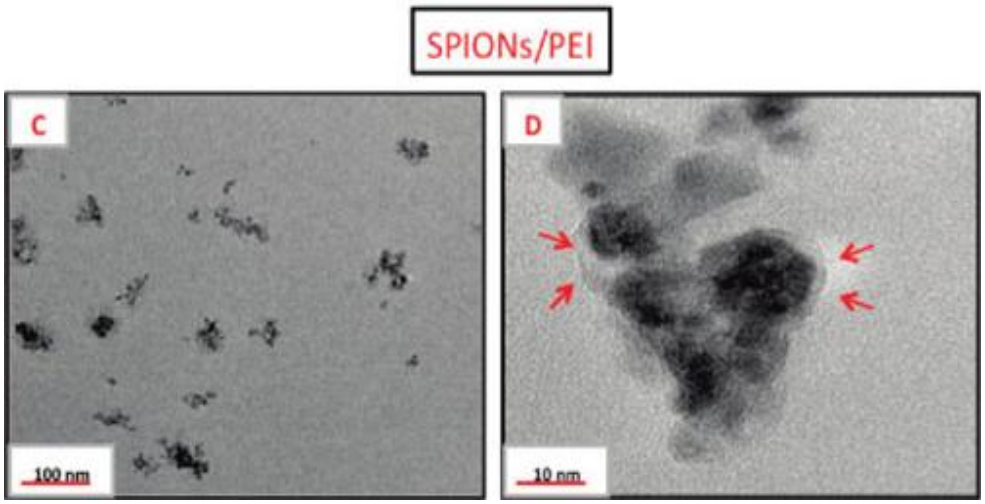


Figure 1 : TEM images of (A,B) as-synthesized SPIONs and (C,D) SPIONs/PEI (ratio = 10) at pH 4 displaying better dispersion (arrows indicating layer of adsorbed PEI)[24]

(Courtesy of Berger, 2011)

Vaccines are often the most cost-effective tools for public health. They have historically contributed to a reduction in the spread and burden of infectious diseases and have played the major part in previous elimination campaigns for these diseases. A completely effective vaccine is not yet available for malaria, although several vaccines are under development. SPf66 was tested extensively in endemic areas in the 1990s, but clinical trials showed it to be insufficiently effective.[25] Other vaccine candidates, targeting the blood-stage of the parasite's life cycle, have also been insufficient on their own.[25] Several potential vaccines targeting the pre-erythrocytic stage are being developed, with RTS, S showing the most promising results so far.[26]

Malaria diagnosis

The objectives of malaria diagnosis are it should be rapid, the report should be available within one hour of arrival of case, and it should be highly sensitive and specific. It is not important only to detect parasite in blood but it is also important to count their number and identify complication of severe forms of malaria. Malaria can be diagnosed by clinical features and parasitological diagnosis with light microscopy and rapid diagnostic tests.[27] This involves identification of malaria parasite or its antigens/products in the blood of the patient. Although this seems simple, the efficacy of the diagnosis is subject to many factors. The different forms of the four malaria species; the different stages of erythrocytic schizogony; the endemicity of different species; the population movements; the inter-relation between the levels of transmission, immunity, parasitemia, and the symptoms; the problems of recurrent malaria, drug resistance, persisting viable or non-viable parasitemia, and sequestration of the parasites in the deeper tissues; and the use of chemoprophylaxis or even presumptive treatment on the basis of clinical diagnosis can all have a bearing on the identification and interpretation of malaria parasitemia on a diagnostic test.[28]

The diagnosis of malaria is confirmed by blood tests and can be divided into microscopic and non-microscopic tests. Conventional microscopic diagnosis involves staining thin and thick peripheral blood smears and Quantitative Buffy Coat (QBC) test , some advantages and shortcomings of these methods have also been described, related to sensitivity, specificity, and accuracy, precision, time consumed cost-effectiveness, labor intensiveness, the need for skilled microscopists, and the problem of inexperienced technicians.[29] Several attempts have been made to take the malaria diagnosis out of the realm of the microscope and the microscopist. Important advances have been made in diagnostic testing, including fluorescence microscopy of parasite nuclei stained with acridine orange, rapid dipstick immunoassay, and Polymerase Chain Reaction assays. These tests involve identification of the parasitic antigen or the antiplasmodial antibodies or the parasitic metabolic products. Nucleic acid probes and immunofluorescence for the detection of *Plasmodia* within the erythrocytes; gel diffusion, counter-immunoelectrophoresis, radio immunoassay, and enzyme immunoassay for malaria antigens in the body fluids; and hemagglutination test, indirect immunofluorescence, enzyme immunoassay, immunochromatography, and Western blotting for anti-plasmodial antibodies in the serum have all been developed. These tests have found some limited applications in research, retrograde confirmation of malaria, investigation of cryptic malaria, transfusion blood screening, and investigation of transfusion acquired infections.[30]

There is an urgent need in the developing world for better disease diagnosis, and nanotechnology offers a multitude of options for detecting disease. Fluorescent quantum dots could also be used to diagnose malaria by making them target the protein that forms a mesh in the blood cell's inner membrane. The shape of this protein network changes when cells are infected with malaria, so scientists are able to spot malaria infection from the shape produced by the dots [31] as shown in Fig 2.

Figure 2: This picture shows dark orange-stained malaria parasites inside red blood cells (a) and outside the cells (b). Note the large cells that look like targets; it is unknown how these target cells are related to this disease.[31]

(Adopted from Tokumasu *et al*., 2005)

Researchers have created a credit-card sized tool; this can be stored for months and then used to test for malaria--part of a larger project to develop high-tech tools for global health. The prototype dehydrated the reagents to store them without refrigeration, and delivered a diagnosis in just nine minutes.[32]

Antimalarial drug resistance

Antimalarial drug resistance has been defined as the "ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject".[33] The important factors that are associated with resistance are: 1. longer half-life. 2. Single mutation for resistance. 3. Poor compliance 4. Host immunity. 5. Number of people using these drugs.[34]

The characteristics of a drug that make it vulnerable to the development of resistance are: a long terminal elimination half-life, a shallow concentration-effect relationship, and mutations that confer marked reduction in susceptibility. There is now circumstantial evidence that the development of resistance can be delayed by combining a well-matched drug pair, i.e. combining one drug that rapidly reduces parasite biomass with a partner drug that can remove any residual parasites.[35] Recent genetic and genomic advances have paved the way for discoveries into the origins and spread of antimalarial drug resistance and the underlying molecular mechanisms. Molecular studies tracking the presence of drug resistant determinants in the malarial population can thus provide critical data complementing clinical observations. New genetic tools give us an unprecedented ability to track new mutations as they arise, confirm their importance and mode of action in the laboratory, and measure their prevalence in the population.[36]

Treatment of malaria

The reemergence of malaria in many parts of the world is due to the rapid increase of resistance to most of the available antimalarial drugs, as well as resistance of vectors to insecticides.[37, 38] Drug resistant strains of P. falciparum have been found in many endemic areas of the world and many of conventional antimalarial drugs have been associated with treatment failure. Therefore, there is an urgent need to discover and develop new, effective and safe drugs for the treatment of this disease.[39] Plants from different botanical sources have been used by various traditional medical practitioners (TMPs) for the treatment and cure of malaria.[40] For example quinine and artemisinin have been derived from traditional medicine and plant extracts.[41] About 80% of the populations of many developing countries still use traditional medicines for their health care. Over 90% of Nigerians in rural areas and about 40% of the population living in urban areas depend partly or wholly on traditional medicines.[41] Due to economic reasons, most of the people in developing countries are precluded from the luxury of access to modern therapy. This has made the people to rely on plant and animal resources for their health care over centuries . Furthermore, several studies have been undertaken to evaluate not only the inhibitory effects of various plant extracts on *P. falciparum* using *in vitro* culture, but also *in vivo* anti-malarial properties on *Plasmodium berghei*-infected mice.[38] Natural antimalarial products have traditionally provided most of the antimalarial drugs in use, with the achievements of synthetic chemistry and the advances towards rational antimalarial drug design, herbal antimalarial drugs continue to be essential in providing antimalarial medicinal compounds and as starting points for the development of antimalarial synthetic analogues. However, to ensure the safety of these herbal antimalarial drugs, there must be adequate information on the contra-indications, drug interactions and toxicities of these drugs and there should also be proper standardization and clinical trials of these plant products.[39]

Artemisinin Combination Therapy (ACTs) has been recommended as first line therapy for the treatment of uncomplicated malaria. Artemisinin derivatives used as monotherapy is no longer encouraged as WHO in order to preserve the efficacy of artemisinins as an essential component of life-saving ACTs, has called for a ban on the use of oral artemisinin monotherapies at various levels including manufacturers, international drug suppliers, National health authorities and funding agencies involved in the funding of essential antimalarial medicine.[21] Efforts should also be made to decrease inappropriate treatment and delay the emergence of resistance to ACT while enhancing the delivery of ACT for malaria treatment [42], therefore there is need for nanomedicine strategies in malaria treatment.

Various strategies to deliver antimalarials using nanocarriers have been evaluated. However, taking into

account the peculiarities of malaria parasites, the focus is placed mainly on lipid-based (e.g., liposomes, solid lipid nanoparticles and microemulsions) and polymer-based nanocarriers (nanocapsules and nanospheres) as shown in Fig 3.[43]

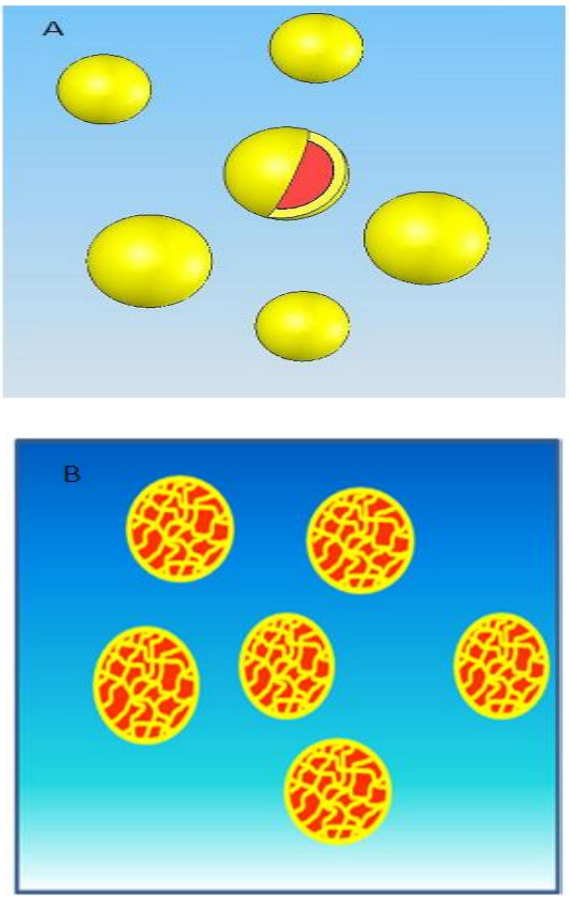


Figure 3: Schematic illustration of polymeric particles. A= Nanocapsules, B= Nanospheres.[43]
(Adopted from Boiturnelo *et al*., 2010)

These nanocarriers are known to improve the efficacy of currently available antimalarial drugs and also contribute to the formulation and delivery of new chemical entities.[43] The previously discussed physicochemical properties of carrier allow for improved intracellular uptake and minimises the first pass metabolism of these drugs, thus improving the overall bioavailability. Targeting drugs specifically to their site of action has great advantage in malaria since malaria parasites frequently develop drug resistance due to the administration of low drug concentrations in the presence of a high parasitic count. Furthermore, nanomedicine has the potential to restore the use of old and toxic drugs by modifying their biodistribution, improve bioavailability and reducing toxicity.[43] This advantage is particularly important in malaria therapy, since the development of new dosage forms for delivering drugs to parasite infected cells is urgently needed, especially for the antimalarials in clinical use.[44]

CONCLUSION

Research into new medications, insecticides, and vaccines will be required to achieve the eventual goal of eradication. Tight control of the regulatory environment to ensure provision of high-quality drugs and appropriate dosing advice will be vital to promoting compliance and preserving effectiveness of ACT. Also the search for additional antimalarials from higher plants must continue to fight the disease. Proper management of malaria would also play a very important role in saving lives, reducing morbidity, breaking the chain of transmission and preventing the development of drug resistance.

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