J Pediatr Rev. 2013;1(1)19-33

JPR
Journal of Pediatrics Review
Mazandaran University of Medical Sciences

Malaria in Children, Prospects and Challenges

Mohammad Sadegh Rezai[1]
Ahmad Ali Enayati[2*]
Janet Heamingway[3]

[1]Department of Pediatric Infectious Diseases, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[2]School of Public Health and Health Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[3]Liverpool School of Tropical Medicine, Liverpool, UK

ARTICLE INFO

Article type:
Review Article

Article history:
Received: 16Aug 2012
Revised: 29Nov 2012
Accepted: 15Dec 2012

Keywords:
Malaria, Children, Prospect, Challenge, Iran

http://jpr.mazums.ac.ir

ABSTRACT

Malaria is still the number one killer especially among the young children and is responsible for one death per minute in the world. Overall, between 250-500 million cases of the disease occur worldwide causing more than one million deaths annually about 90% of which in children under five years of age. Although the spread of the disease is worldwide but it is seen mostly in tropical and subtropical regions of all continents and is more so in sub-Saharan Africa. Five parasite species transmitted by more than 70 potent Anopheles mosquito vectors are responsible for the occurrence of the disease and its spread. There have beenseveral approaches for malaria diagnosis, management and prevention as a whole and in children (as the most vulnerable group) in particular with various degrees of success. In this context works undertaken by international organizations such as Roll Back Malaria, Global Fund, UNICEF, as well as None for Profit international agencies and also at the national levels are promising in malaria control. However, drug and insecticide resistance, constraints in access to health care, poverty and the like are among the main challenges ahead. In this review paper the situation of malaria and its management measures with especial reference to children are discussed.

Introduction

Malaria is still the most important infectious disease in the world, inflicting 250-500 million people claiming the lives of about one million. In other words, almost half the world's population lives in countries where the disease is endemic, and almost every country in the world encounters imported malaria.[1, 2] More than 90% of the cases occur in Sub-Saharan Africa where the majority of the cases (more than 90%) are composed of children aged 6 months to 5 years.[1, 3] Children are considered as one of the main vulnerable groups as they are naive immunologically for malaria parasite especially the most potent of which Plasmodium falciparum.[4] The disease may cause as many as 10% of all deaths in children.[1]

**Corresponding Author: AhmadaliEnayati, Professor, PhD of Medical Entomology*
Mailing Address: Vice Chancellor for Research and Technology, Moallem Sq. Moallem St. Sari, Mazandaran Province, Iran
Tel: +98 151 3257230
Fax: +98 151 3261244
Email: aenayati@mazums.ac.ir

Burden of Malaria

In 1900, more than 77% of the world population in 140 countries were at risk of malaria[5] and the mortality rate at the time was 19.4 per 10,000 population. In Africa, the infant malaria specific mortality rate was 9.5 per 1000 prior to 1960 [6], though this statistics dramatically reduced to 1.61 per 10,000 by 1970. [7]

According to the World Malaria Report published in 2011, there were 655,000 malaria deaths worldwide in 2010, compared to 781,000 in 2009.[1] It has been estimated that 91% of deaths in 2010 were in the African Region, followed by the South-East Asia (6%) and Eastern Mediterranean Regions (3%). About 86% of deaths globally were in children under 5 years of age.[1] However, in a recent research, it was revealed that the World health organization(WHO) estimate was in fact an underestimation and it is closer to reality that 1.24 million people died from malaria in 2010.[2]

Malaria in Iran

There are eight Anopheles species transmitting the disease in Iran the most important of which are An. stephensi and An. culicifacious. The most frequent parasites are P. Vivax and P. Falciparum leaving the third species, P. Malaria, consisting only 3-4%.[8] The situation of malaria in Iran before the Global Malaria Eradication Campaign (GMEC) was so that except the deserts, all areas were endemic with high annual incidence.[8] However, after the campaign, the disease has been marginalized to the southern and more so to the south eastern parts of the country. The number of cases in Iran was about 100 thousand a decade ago, but it has dropped since and reached under 10 thousand in recent years.[9] The total number of confirmed cases in 2010 was 3031 of which 1847 were locally acquired and 1184 were imported cases.[1] Iran moved to the elimination stage in 2010, and adopted a nation-wide elimination strategy in that year.[1]

Malaria in Mazandaran

Malaria in Mazandaran is under control since the end of the GMEC in 1967.[8, 10] The total number of cases from 1997 to 2012 was 844, of which 822 P. vivax, 16 P. falciparum and 1 P. malaria. Of 844 cases, 641 were imported. Unlike the usual trend, the majority of the cases are adults. Babulsar and Tonekabon followed by Amol reported the highest number of the cases.[10]

There are many reasons why the situation of malaria in the south and north being more or less the same before the GMEC, are now so different. They include: higher number of more potent Anopheles species often with multi insecticide resistance in the south compared with the north; presence of more potent drug resistant P. falciparum only in the south; significant differences in terms of the socioeconomic and cultural characteristics of the two regions (this has a direct impact on the compliance with the malaria elimination efforts); lack of adequate public health infrastructure and access to health care; longer transmission season; border problem with endemic areas of Pakistan and Afghanistan.[8]

Malaria transmission

Mosquito bite

The disease is exclusively transmitted through the bite of female Anopheles mosquitoes that occurs between dusk and down. More than 400 species of Anopheles exist in the world but only about 70 species are vectors and only 30 of which are more important and potent.[11] After one exoerythrocytic and a few cycles of erythrocyticschizogony, some merozoites differentiate into the male and female gametocytes. Upon taking a blood meal from a patient with gametocytemia, the female mosquito acquires these sexual forms and plays

host to the sexual stage of the plasmodial life cycle. After 10-12 days and completing the sporogony, sporozoites are transmitted to a new human host through an infectious bite of a female mosquito.[12, 13]

Blood transfusion

Blood transfusion is also a relatively important route especially in malarious areas. In these endemic areas, semi-immunity to malaria allows donors to have parasitemia without any fever or other clinical manifestations [14]. In this case, transmission is by merozoites, which do not enter the liver cells, hence curing the acute attack results in complete cure due to the lack of hypnozoites.[12]

Congenital malaria

Prenatal or perinatal transmission of malaria from a nonimmune mother to the fetus or baby is called congenital malaria. It may cause abortions, miscarriages, stillbirths, premature births, intrauterine growth retardation, and neonatal deaths. The signs or symptoms usually occurring a couple of weeks after birth include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly.[4, 15]

Cryptic malaria

The category of cryptic malaria includes cases for which no source of infection can be identified. Airport malaria, one kind of cryptic malaria, occurs in proximity to international airports.[16]

Other routs of malaria transmission

Malaria also can be transmitted through the use of contaminated needles. [4, 17] Organ transplantation is another malarial transmission route.[18]

Malaria parasitology

There are five species of malaria parasites including P. falciparum which is the predominant species in Africa, central America, Indian Subcontinent, and southeast Asia, P. vivax predominates in the Mediterranean region, Bangladesh, Central America, India, Pakistan, and Sri Lanka, P. malaria predominate in Southeast Asia, South America, and Oceania, P. ovale and P. knowlesi (the least common species) are transmitted primarily in Africa.[19,4] Most malaria cases acquired in Africa are due to P. falciparum. P. vivax dominates in Asia and the Americas.[1]

In Iran, P. falciparum dominates in the south plus P. vivax and P. malariae malaria, while P. vivax is the only parasite species in the north.[8]

Malaria symptoms

There is no symptoms during the exo-erythrocyticshizogony period and also the first round of erythrocyticshizogony. This period depends on the species of the parasite and is usually 9-14 days for P. falciparum, 12-17 days for P. vivax, 16-18 days for P. ovale, and 18-40 days for P. malariae. The classical clinical manifestations of malaria include shiver and chill for about one hour followed by a period of about 6 hours of high temperature coupled with flushed skin, headache, body ache, fatigue, nausea and vomiting, diarrhea and a final phase of sweet lasting for about 4 hours.[4]Spleenomegaly, hepatomegaly, jaundice, anemia, thrombocytopenia, acute kidney failure and pulmonary distress are among other important symptoms of malaria. The patient feels relatively well between the episodes of the disease.[4]

The periodicity of malarial fever and other symptoms depends on the time required for the erythrocyticshizogonyand is definite for each species. P. malariae needs 72 hours for each cycle, hence the name quartan malaria (three days without high fever followed by one day showing the symptoms). P. vivax and P. ovale take 48 hours for one cycle and cause fever every two days (tertian malaria). P. falciparum

and P. knowlesi require only 24 h for their cycles to complete; hence the patient feels the symptoms every other day.[12] However, in case of mixed infection and also the parasites not being synchronized, this periodicity may not be observed.

Severe malaria

Although there is not a gold standard for the definition of severe malaria, it is considered severe if the following WHO criteria are present: Impaired consciousness, prostration, respiratory distress, multiple seizures, jaundice, hemoglobinuria, abnormal bleeding, severe anemia, circulatory collapse and pulmonary edema.[4] The criteria in children emphasize more on consciousness, severe anemia, and respiratory distress.[20] Malaria caused by P. vivax is usually mild and rarely life threatening compared with P. falciparum , however recent reports suggest that in some areas of Indonesia it caused severe disease and death as P. falciparum mainly due to severe anemia and sometimes to splenic rupture.[21]

Malaria Diagnosis

Classic method

The gold standard of malaria diagnosis is by microscopic examination of Giemsa-stained thick or thin smear of peripheral blood despite advances in immunological and molecular techniques.[12, 22] Thick smear allows scanning large number of erythrocytes for a rapid diagnosis of infection and thin smear helps in establishing the species of the parasite.[4]

Polymerase Chain Reaction

Although morphologically distinguishable, PCR strategies have been developed to diagnose P. falciparum and P. vivax[23]. However, P. knowlesi and P. malariaecannot be diagnosed morphologically, therefore, polymerase chain reaction may be helpful.[4, 24]

Rapid test

Immunochromatographic tests based on the capture of the parasite antigens from the peripheral blood using either monoclonal or polyclonal antibodies against the parasite antigen targets have been developed in the last decade to facilitate the diagnosis of malaria where proper microscopy is not possible and basic laboratory materials and equipments are not available. Currently, immunochromatographic tests can target the histidine-rich protein 2 of P. falciparum, a pan-malarial Plasmodium aldolase, and the parasite specific lactate dehydrogenase.[25-27]

Antibody detection

Malaria antibodies have limited value in diagnosing malaria in individual patients. That may have a role in the diagnosis of hyperactive malarial syndrome.[28]

Differential diagnosis

Due to the nature of the signs and symptoms of malaria, the differential diagnosis of malaria includes viral infections such as influenza and hepatitis, sepsis, pneumonia, meningitis, meningoencephalitis, encephalitis, gastroenteritis, brucellosis, Kala-azar, Schistosomiasis, Acute MyelocyticLeukemia, leptospirosis, tuberculosis, relapsing fever, typhoid fever and yellow fever. [25, 28],[4] There is also considerable clinical overlap between septicaemia, pneumonia and severe malaria. As it is often impossible to rule out septicaemia in a shocked or severely ill obtunded child, where possible, blood should always be taken on admission for culture, and if there is any doubt, empirical antibiotic treatment should be started immediately along with antimalarial treatment.[25]

Complications of malaria in children

The most common complications in children are severe anemia.[29,30] impaired consciousness (including cerebral malaria)[31], respiratory

distress (due to metabolic acidosis) [32, 33], multiple seizures[34-36], Black Water Fever and jaundice [37] leading to poor prognosis. [3839]In any case, it does not justify the underestimation of the risks posed by P. vivax as new case studies revealed that this latter is not far behind the former in causing severe malaria especially in young children.[40, 414]

Malaria management

Malaria can be prevented and once contracted should be treated[1] and in fact treatment of the disease is also a method of prevention as it prevents the mosquitoes to get infected while blood feeding from the ill individual.[42]

Vector Control

Applying indoor residual spraying (IRS) and distribution of long lasting insecticide treated bednets (LLINs) are generally applicable for reducing disease transmission.[42]

a) Indoor Residual Spraying (IRS)

IRS is defined as the application of stable formulations of insecticides on the inside of houses to kill mosquitoes that come in contact with.[4342, 44]

Application of non-residual formulations like aerosols in houses especially children's bedrooms before retiring at night is also recommended for temporary malaria control.[45, 46] It is recommended to apply the spray well before the children are put in the room to sleep to reduce the risk even further.

b) Insecticide treated nets (ITNs)

Although untreated bednets have been used for mosquitoes nuisance as well as malaria control, [11, 47-54] but ITNs are far more effective than untreated nets in reducing malaria especially in children less than 5 years of age.[47]Pyrethroids are the insecticides of choice for treatment due to their low mammalian toxicity. They are extremely safe for household use and even if an infant chews a relatively large area of the treated netting, it would not exceed the maximum daily intake level.[55]

To be of maximum effectiveness, bednets should be used properly and in the right time and place. In doing so, bednets should be tucked in under the mattress, vulnerable groups especially children should be under the bednets early in the night and care must be taken to avoid contact of bare arms and legs to the nets as mosquitoes can blood feed from them against the nets.[56]

Repellents

Different chemicals such as Diethyl-meta-toluamide(DEET)in formulations like spray, cream, lotion and fumigants are commercially available to be used personally to keep the mosquitoes away. Application of every 3-4 hours of any formulation of DEET less than 40% to exposed areas of skin except eyes and mouth is recommended. In infants, hands are frequently put in mouth, so they are not to be treated.[57-60]

Chemoprophylaxis and intermittent presumptive therapy

Chemoprophylaxis and intermittent presumptive therapy (IPT) are available to control malaria.[61-63] Chemoprophylaxis, which is defined as subtherapeutic doses of an antimalarial drug, and IPT, the use of full treatment doses of drugs given at a few pre-specified time points are chemoprevention methods available. IPT is given to pregnant women and is being considered for infants and children in areas of high transmission where many will be infected.[3] The drugs used for the chemoprophylaxis of malaria are given in Table 1. [64]

Treatment

There are several different categories of drugs for malaria treatment including those with

blood schizontocidal effects e.gchloroquine and amodiaquine, and primaquine with gametocidal effect as well as activity against hypnozoites. [40, 65-67]

The artemisinin- derivative drugs such as artemether, arteether and artesunate have recently been commercialized [68] and used in malaria management worldwide.[69] Their effectiveness in combination with other classic antimalarials is documented by several studies in different settings.[70-74]

Malaria treatment in Iran

Based on the WHO recommended treatment for malaria, IranianCenters for Disease Control and Prevention (CDC) issues and updates guidelines for malaria treatment is summarized in Table 2. Information is given for pediatrics malaria treatment only.

Malaria immunity

Although incomplete, immunity acquired by individuals after contracting the disease especially in endemic and hyperendemic areas may prevent severe disease but still allowing future infection. Individuals with sickle cell anemia and thalassemia resist malaria, erythrocytes lacking Duffy blood group antigen are resistant to P. vivax, and erythrocytes containing hemoglobin F (fetal hemoglobin) are resistant to P. falciparum. The latter plus the passive maternal antibody, are the reasons why newborns rarely become ill with malaria in hyperendemic areas.[75] Children 3 mo to 2-5 yr of age have little specific immunity to malaria species and therefore the disease takes most of its toll from this group of children in hyperendemic areas. Immunity is subsequently acquired, and severe cases of malaria become less common.[4]In areas of intense malaria transmission, most cases of severe malarial anemia and deaths occur in infants and young children because of their exposure and lack of immunity.[3, 76] In stable transmission areas, the major effect is malaria-related anemia in the mother and presence of parasites in the placenta resulting in low-birth weight which contributes substantially to child deaths.[77] As vulnerable groups, young children (under 5 years) and pregnant women should be at the centre of malaria control programmes in highly endemic areas.[3]

Vaccines

Development of an effective malaria vaccine has been a longstanding but difficult objective. There are three parasite stages targeted by malaria vaccine development programs including a) pre-erythrocytic vaccines which target the sporozoites to prevent them from invading hepatocytes (neutralizing antibody) or to destroy them once inside the hepatocytes [78], b) Blood stage vaccines which inactivate the merozoites during the relatively short time that they are in the blood stream, or target malaria antigens expressed on the surface of red blood cells [78-80], c) Transmission-blocking vaccines which prevent from the sexual stage of the parasite [81] and d) Anti P. vivax malaria vaccine with only two vaccine candidates being tested in preliminary clinical trials.[82]

The 1st malaria vaccine to have any degree of efficacy is the RTS'S vaccine, which is based on the circumsporozoite protein of P. falciparum. In various clinical trials, this vaccine has shown an efficacy of 26-56% against uncomplicated malaria and 38-50% against severe malaria in young children in malaria endemic areas in periods as long as 45 mo after vaccination. The vaccine is now in large phase III trials. [4, 83, 84]

Prospects of malaria control

Roll Back Malaria (RBM) Partnership

RBM Partnership was announced by WHO in 1998, with the goal of halving malaria deaths by 2010, and halving it again by 2015 by a) strengthening the aggressive control of malaria in its heartland, b) shrinking the malaria map from the endemic margins inward and c) continue researching and developing new tools, such as improved drugs, diagnostics,

insecticides, and eventually a vaccine.[85, 86] International organizations such as the WHO, World Bank, UNDP and UNICEF as well as international donors plus 20 African Heads of State in Abuja, Nigeria in April 2000 pledged international and African commitment to malaria control.[86, 87] Although this was an enthusiastic programme, in practice adequate resources has not gone through the plan of action, therefore the goals were never achieved.[86]

Millennium Development Goals

This covers a whole host of different goals including malaria. Target 6C indicates that malaria transmission should be halted by 2015 and begun to reverse the incidence of malaria and other major diseases. [88, 89] Management of other diseases such as HIV by providing NNRT drugs reduced the incidence and recurrence of malaria.[90] Based on WHO world malaria report in 2011, there were 655 000 malaria deaths worldwide in 2010, compared to 7,81,000 in 2009.[1] However in a recent research it was revealed that 1.24 million people died from malaria in 2010. [2]

Global Malaria Action Plan

By 2010, 80% of people at risk from malaria should use locally appropriate vector control methods such as LLINs and IRS. 80% of malaria patients should be diagnosed and treated with effective anti-malarial treatments; and the global malaria burden should be reduced by 50% from 2000 levels: to less than 175-250 million cases and 500,000 deaths annually from malaria.

By 2015: through universal coverage with effective interventions, global and national mortality is near zero and global incidence is reduced to less than 85-125 million cases per year; the incidence is halted and begun to reverse by 2015.

Beyond 2015:Malaria mortality stays near zero through universal coverage for all populations at risk, and countries currently in the pre-elimination stage will achieve elimination.[91]

Bill and Mellinda Gates Foundation and Innovative Vector Control Consortium (IVCC)

Like several other international charitable and non-for-profit organization, IVCC sponsored by Bill and Mellinda Gates Foundation is committed to research and development in malaria control aiming at producing new tools like LLINs, new insecticide molecules as well as a front for malaria vaccine among other programmes.[92]

Member States Commitment to Malaria Elimination

The 23 countries of the Eastern Mediterranean Region are in various stages of malaria control: seven still have areas of high malaria transmission and are in the control stage (Afghanistan, Djibouti, Pakistan, Somalia, Sudan, South Sudan, and Yemen); two countries with geographically limited malaria transmission are in the elimination stage (the Islamic Republic of Iran, and Saudi Arabia). Egypt, Oman and the Syrian Arab Republic are in the prevention of reintroduction stage and the remaining countries are malaria-free.[1]

Challenges Facing Malaria Control

Drug resistance

Chloroquine resistance was first reported in P. falciparum from Colombia and Thailand in 1960 [93], leading to complete loss of effectiveness in many high-transmission areas in 1980s. Latter resistance extended to other antimalarials such as sulphadoxine-pyrimethamine.[94] As a result, artemisinin derivatives have been introduced in recent years but the first cases of artemisinin resistance have already been reported in Cambodia.[95, 96]

Insecticide resistance

The phenomenon is caused by several different mechanisms including biochemical or site insensitivity [11, 42] through producing qualitatively or quantitatively different enzymes that detoxify insecticide molecules [97] or changes in the receptors of insecticide molecules so that they are no longer susceptible to them.[98] As pyrethroid insecticides are the only group available for ITNs and LLINs, pyrethroid resistance has particularly different impacts on the personal protection provided by ITNs.[48, 99-106]

Mobile population

Mobile populations usually live in temporary shelters where mosquitoes may enter readily. In these situations, personal protection is of high importance especially for more vulnerable groups like pregnant women and children.[107-109]

Refugees

Displaced people are at higher risk of a whole host of infectious diseases including malaria as the health infrastructure is no longer present and the means of malaria protection may not be available. The refugees are even more vulnerable to diseases as the situation may reduce the immunity and the physical, physiological and immunity vigor.[107-109]

Border malaria

Being neighbor to malaria endemic countries and cross-border malaria is a challenge in malaria management. Iran has common borders with Afghanistan and Pakistan in the east and with several Persian Gulf states in the south which makes the country vulnerable to border malaria through immigrants (mostly illegal) crossing the border. The parasites they carry are often resistant to most antimalarial drugs. [8]

Disasters and civil unrest

The consequence of these situations are lack of health infrastructure, modifications in the ecological conditions that may result in changes in the populations and behavior of vectors including mosquitoes, reduction in the immunity level and the physical, physiological and immunity vigor of the people especially children, which make individuals especially children and even more so girls more prone to malaria.[107, 110]

Community resistance

In many societies interventions such as IRS, ITNs and IPT face resistance for different reasons. IRS especially after several years of operation, is not welcome as it requires preparations in the houses, it may alter the color of the walls and also has bad smell. ITNs may not be accepted as they may block the free air stream which is a problem in tropical weather. IPT may not be accepted due to fear of side effects.[111] Though behaviors like feeling obliged for receiving health care such as vaccine may pave the way for implementing one when available. [112]

Access to healthcare and socioeconomic issues

In many regions of the world populations in remote areas lack adequate access to healthcare as communities are small and scattered and appropriate road is lacking.[112] Another problem is gradual transition from free healthcare to more private sector healthcare which seeks community partnership. Poverty is another issue [113-115] and most communities resist this privatization by not acquisition of the care owing to their economic status.[116] Literacy level is a major determinant in seeking healthcare.[117]

Forest malaria

Forest malaria dominates in many parts of Southeast Asia, Africa, and South America and is more difficult to control than non-forest

Table 1. drugs used for the chemoprophylaxis of malaria

Drug	Usage	Pediatric dose	Comments
Atovaquone/ proguanil (MALARONE)	Prophylaxis in all areas	Pediatric tablets (62.5 mg atovaquone/25 mgproguanilHCl). 5-8 kg: 1/2 ped tab/day >8-10 kg: ¾ ped tab/day >10-20 kg: 1 ped tab/day >20-30 kg: 2 ped tab/day >30-40 kg: 3 ped tab/day >40 kg: 1 adult tablet daily	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in persons with severe renal impairment (creatinine clearance <30 mL/minute).
Chloroquine phosphate (ARALEN and generic)	Prophylaxis only in areas with chloroquine sensitive malaria	5 mg/kg base (8.3 mg/kg salt) orally, once/week, up to max adult dose (300 mg base)	Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in themalarious area and for 4 weeks after leaving such areas.
Doxycycline	Prophylaxis in all areas	8 years of age: 2 mg/kg up to adult dose of 100 mg/day	Begin 1-2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in children <8 years of age and pregnant women.
Hydroxychloroquine sulfate (PLAQUENIL)	An alternative to chloroquine for prophylaxis only in areas with chloroquinesensitivemalaria	5 mg/kg base (6.5 mg/kg salt)orally,once/week, upto max adult dose (310 mgbase)	Begin 1-2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas.
Mefloquine (LARIAM and generic)	Prophylaxis in areas with mefloquine sensitive malaria	9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once/week; >9-19 kg: ¼ tablet once/week; >19-30 kg: ½ tablet once/week; >31-45 kg: ¾ tablet once/week; 45 kg: 1 tablet once/week	Begin 1-2 weeks before travel to malarious areas. Take weekly on same day of the week while in malarious area and for 4 weeks after leaving suchareas.
Primaquine	Prophylaxis for short duration travel to areas with principally P. vivax	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	Begin 1-2 days before traveltomalarious areas. Take daily at same time each day while in malarious area and for 7 days after leaving suchareas. Contraindicated in persons with G6PDa deficiency, and during pregnancyand lactation unless the infant being breastfed has documented normal G6PD level.
Primaquine	For presumptive anti-relapse therapy (terminal prophylaxis) to decrease the risk of relapses (P. vivax, P.ovale)	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, once/day for 14 days after departure from the malarious area	Indicated for persons who have had prolonged exposure to P. vivax and P. ovale or both. Contraindicated in persons with G6PDa deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level.

malaria. The vectors are often partially or wholly exophilic and exophagic and do notnormally enter houses protected by IRS or LLINs. The situation particularly in India, with54 million population involved, in Vietnam in16 out of 64 provinces, in Bel´ em, Par´ a, a forest fringe area of Brazil, in the forested areas of equatorial Africa, in Thailand, Cambodia, and Vietnam is now a major problem.[11]

Table 2. Iranian CDC guideline for pediatric malaria treatment

Clinical diagnosis/species	Drug resistance status	Pediatric dose
Malariae and vivax	Susceptible to Chloroquine	Chloroquine: Day 1: 10 mg/kg Day 2: 10 mg/kg Day 3: 5 mg/kg Primaquine: 0.25 mg/kg/day for 14 days Or 0.75 mg/kg/week for 8 weeks
Uncomplicated falciparum malaria, first line of treatment	Chloroquine resistance	Day 1: Artesunate 4 mg/kg plus fansidar 25 mg/kg Day 2: Artesunate 4 mg/kg Day 3: Artesunate 4 mg/kg
Uncomplicated falciparum malaria, if artesunate and Coartem are not available	Chloroquine resistance	Chloroquine: Day 1: 10 mg/kg plus 25 mg/kg fansidar Day 2: 10 mg/kg Day 3: 5 mg/kg plus Primaquine 0.75 mg/kg
Uncomplicated falciparum malaria, second line of treatment (first line of treatment failure)	Chloroquine resistance	Coartem 5-15 kg: one tab po bid for 3 days 15-25 kg: two tabs po bid for 3 days 25-35 kg: 3 tabs po bid for 3 days >35 kg: 4 tabs po bid for 3 days
Uncomplicated falciparum malaria, third line of treatment (second line of treatment failure)	Chloroquine resistance	Quinin 10 mg/kg (max 800 mg) tid for 3 days Plus Clindamycin 10 mg/kg did for 7 days
Severe falciparum malaria	Chloroquine resistance	Quinin 15 mg/kg first IV dose followed by 10 mg/kg tid for 3 days
Severe falciparum malaria	Chloroquine resistance	Artesunate 2.4 mg/kg every 12 hours for three doses followed by once daily for 3 days

Conclusion

There have been several ups and downs to malaria management since its discovery in the early 20th century. Major successes were in the sanitation period in the middle of the 20th century followed by the GMEC in the 60s and 70s and finally by RBM and Millennium Development Goals supported by several international organizations. During the years, the diagnosis, treatment, control and management of the disease have dramatically improved. Although there are several challenges such as drug and insecticide resistance as well socioeconomic and behavioral issues, the prospect of malaria management is promising through scientific discoveries of new tools and techniques in malaria management, international cooperation and community participation in implementing the interventions of malaria control.

Conflict of Interest

None declared.

Funding/Support

None declared.

References

1. WHO. World malaria report Switzerland; 2011.
2. Murray CJ, Rosenfeld LC, Lim SS, Andrews KG, Foreman KJ, Haring D, et al. Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 2012; 379(9814): 413-31.
3. Hsiang MS, Panosian C, Dorsey G. Understanding Malaria. In: Feachem RGM, Phillips AA, Targett GA, editors. Shrinking the Malaria Map a Prospectus on Malaria Elimination. San Francisco: The Global Health Group; 2009. p. 81-94.
4. Krause PJ. Malaria (Plasmodium). In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson Textbook of Pediatrics. 17th Edition ed: Saunders; 2011. p. 1139-43.
5. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. The Lancet Infectious Diseases. 2004; 4(6): 327-36.
6. Snow RW, Trape J-F, Marsh K. The past, present and future of childhood malaria mortality in Africa. Trends in Parasitology. 2001; 17(12): 593-7.
7. Carter R, Mendis KN. Evolutionary and Historical Aspects of the Burden of Malaria. Clinical Microbiology Review. 2002; 15(4): 564-94.
8. Edrissian G. Malaria in Iran: Past and Present Situation. Iranian Journal of Parasitology. 2006; 1(1): 1-14.
9. Mohammadi M, Ansari-Moghaddam A, Raiesi A, Rakhshani F, Nikpour F, Haghdost A, et al. Baseline results of the first malaria indicator survey in Iran at household level. Malar J. 2011; 10: 277.
10. Ghaffari S, Mahdavi SA, Moulana Z, Mouodi S, Karimi-Nia H, Bayani M, et al. Malaria in Mazandaran, Northern Iran: Passive Case Finding During 1997-2012. Iranian J Parasitol. 2012; 7(3): 82-8.
11. Enayati AA, Lines J, Hemingway J. Malaria management, past, present and future. Ann Rev Entomol. 2010; 55: 569-91.
12. Wernsdorfer WH, McGregor I. Malaria: Principles and Practice of Malariology Edinburgh: Churchill Livingstone; 1989.
13. Service MW. Medical Entomology for students. 4 ed. Cambridge: Cambridge University Pressl; 2008.
14. Enevold A, Nkya W, Theisen M, Vestergaard L, Jensen A, Staalsoe T, et al. Potential impact of host immunity on malaria treatment outcome in Tanzanian children infected with Plasmodium falciparum. Malaria Journal. 2007; 6(1): 153.
15. Mwaniki MK, Talbert AW, Mturi FN, Berkley JA, Kager P, Marsh K, et al. Congenital and neonatal malaria in a rural Kenyan district hospital: an eight-year analysis. Malar J. 2010; 9: 313.
16. Karch S, Dellile MF, Guillet P, Mouchet J. African malaria vectors in European aircraft. The Lancet. 2001; 357(9251): 235.
17. Tarantola AP, Rachline AC, Konto C, Houzé S, Lariven S, Fichelle A, et al. Occupational malaria following needlestick injury Emerg Infect Dis 2004 [cited OCT 2004]; Available from: http://wwwnc.cdc.gov/eid/article/10/10/04-0277.htm
18. Rodriguez M, Tome S, Vizcaino L, Fernandez-Castroagudin J, Otero-Anton E, Molina E, et al. Malaria Infection through Multiorgan Donation: An Update From Spain. LIVER TRANSPLANTATION 2007; 13: 1302-4.
19. Barber BE, William T, Jikal M, Jilip J, Dhararaj P, Menon J, et al. Plasmodium knowlesi malaria in children. Emerg Infect Dis. 2011; 17(5): 814-20.
20. Anstey NM, Price RN. Improving Case Definitions for Severe Malaria. PLoS Med. 2007; 4(8): e267.
21. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, et al. Multidrug-Resistant <italic>Plasmodium vivax</italic> Associated with Severe and Fatal Malaria: A Prospective Study in Papua, Indonesia. PLoS Med. 2008; 5(6): e128.
22. Maguire JD, Lederman ER, Barcus MJ, O'Meara WA, Jordon RG, Duong S, et al. Production and validation of durable, high quality standardized malaria microscopy slides for teaching, testing and quality assurance during an era of declining diagnostic proficiency. Malar J. 2006; 5: 92.
23. Mens PF, Moers AP, de Bes LM, Flint J, Sak JR, Keereecharoen L, et al. Development, validation and evaluation of a rapid PCR-nucleic acid lateral flow immuno-assay for the detection of Plasmodium and the differentiation between Plasmodium falciparum and Plasmodium vivax. Malar J. 2012; 11: 279.
24. Sulistyaningsih E, Fitri LE, Loscher T, Berens-Riha N. Diagnostic difficulties with Plasmodium knowlesi infection in humans. Emerg Infect Dis. 2010; 16(6): 1033-4.
25. WHO. Guidelines for the treatment of malaria. Switzerland: WHO; 2006.

26. Bisoffi Z, Gobbi F, Angheben A, Van den Ende J. The Role of Rapid Diagnostic Tests in Managing Malaria. PLoS Med. 2009; 6(4): e1000063.
27. WHO. Malaria Rapid Diagnostic Test Performance. Malta: WHO; 2011.
28. Zingman BS, Viner BL. Splenic complications in malaria: case report and review. Clin Infect Dis. 1993; 16(2): 223-32.
29. Phiri K, Esan M, van Hensbroek MB, Khairallah C, Faragher B, terKuile FO. Intermittent preventive therapy for malaria with monthly artemether–lumefantrine for the post-discharge management of severe anaemia in children aged 4–59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial. The Lancet Infectious Diseases. 2012; 12(3): 191-200.
30. Sowunmi A, Gbotosho GO, Happi CT, Fateye BA. Factors contributing to anaemia after uncomplicated Plasmodium falciparum malaria in children. ActaTropica. 2010; 113(2): 155-61.
31. Holding PA, Stevenson J, Peshu N, Marsh K. Cognitive sequelae of severe malaria with impaired consciousness. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999; 93(5): 529-34.
32. Haydoura S, Mazboudi O, Charafeddine K, Bouakl I, Baban TA, Taher AT, et al. Transfusion-related Plasmodium ovale malaria complicated by acute respiratory distress syndrome (ARDS) in a non-endemic country. Parasitology International. 2011; 60(1): 114-6.
33. Mukherjee T, Lavania AK. Acute respiratory distress syndrome due to vivax malaria. Medical Journal Armed Forces India. 2008; 64(4): 365-6.
34. Kihara M, Carter JA, Holding PA, Vargha-Khadem F, Scott RC, Idro R, et al. Impaired everyday memory associated with encephalopathy of severe malaria: the role of seizures and hippocampal damage. Malar J. 2009; 8: 273.
35. Idro R, Otieno G, White S, Kahindi A, Fegan G, Ogutu B, et al. Decorticate, decerebrate and opisthotonic posturing and seizures in Kenyan children with cerebral malaria. Malar J. 2005; 4: 57.
36. Ikumi ML, Muchohi SN, Ohuma EO, Kokwaro GO, Newton CRJC. Response to diazepam in children with malaria induced seizures. Epilepsy Research. 2008; 82(2–3): 215-8.
37. Silva Lima E, Fabbri C, de CássiaMascarenhasNetto R, Lacerda MVG. Jaundice Is Associated with Oxidative Stress in Patients with Plasmodium Vivax Malaria. Free Radical Biology and Medicine. 2012; 53, Supplement 2(0): S24.
38. Gerardin P, Rogier C, Ka A, Jouvencel P, Diatta B, Imbert P. Outcome of life-threatening malaria in African children requiring endotracheal intubation. Malaria Journal. 2007; 6(1): 51.
39. Achidi E, Apinjoh T, Anchang-Kimbi J, Mugri R, Ngwai A, Yafi C. Severe and uncomplicated falciparum malaria in children from three regions and three ethnic groups in Cameroon: prospective study. Malaria Journal. 2012; 11(1): 215.
40. Reeder JC, Targett GA, Shanks GD, Greenwood BM. Killing the parasite. In: Feachem RGM, Phillips AA, Targett GA, editors. Shrinking the Malaria Map a Prospectus on Malaria Elimination. San Francisco The Global Health Group; 2009. p. 127-39.
41. Ajetunmobi W, Orimadegun A, Brown B, Afolabi N, Olabiyi F, Anetor J, et al. Haemoglobinuria among children with severe malaria attending tertiary care in Ibadan, Nigeria. Malaria Journal. 2012; 11(1): 336.
42. Enayati AA, Lines J, Maharaj R, Hemingway J. Suppressing the vector. In: Feachem RGM, Phillips AA, Targett GA, editors. Shrinking the Malaria Map a Prospectus on Malaria Elimination. San Francisco The Global Health Group; 2009. p. 140-54.
43. Macdonald G. The Epidemiology and Control of Malaria,. Oxford: Oxford University Press; 1957.
44. WHO. Indoor residual spraying, use of indoor residual spraying for scaling upglobal malaria control and elimination. WHO/HTM/MAL/20061112. 2006.
45. Samuelsen H, Toé LP, Baldet T, Skovmand O. Prevention of mosquito nuisance among urban populations in Burkina Faso. Social Science & Medicine. 2004; 59(11): 2361-71.
46. Pemba D, Kadangwe C. Mosquito Control Aerosols' Efficacy Based on Pyrethroids Constituents, Insecticides management/mosquito-control-aerosols-efficacy-based-on-pyrethroids-constituents. In: Perveen F, editor. Advances in Integrated Pest Management: InTech Europe; 2012.
47. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004.
48. Enayati AA, Hemingway J. Pyrethroid insecticide resistance and treated bednets efficacy in malaria control. Pesticide Biochemistry and Physiology. 2006; 84(2): 116-26.
49. Bockarie MJ, Tavul L, Kastens W, Michael E, Kazura JW. Impact of untreated bednets on prevalence of Wuchereriabancrofti transmitted by Anopheles farauti in Papua New Guinea. Medical and Veterinary Entomology. 2002; 16(1): 116-9.
50. Clarke SE, Bogh C, Brown RC, Pinder M, Walraven GE, Lindsay SW. Do untreated bednets protect

against malaria? Trans R Soc Trop Med Hyg; 2001. p. 457-62.
51. D'Alessandro U, Olaleye BO, McGuire W, Thomson MC, Langerock P, Bennett S, et al. A comparison of the efficacy of insecticide-treated and untreated bednets in preventing malaria in Gambian children. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1995; 89: 588-95.
52. Lindsay SW, Shenton FC, Snow RW, Greenwood BM. Responses of Anopheles gambiae complex mosquitoes to the use of untreated bednets in The Gambia. Med Vet Entomol. 1989; 3(3): 253-62.
53. Mwangi TW, Ross A, Marsh K, Snow RW. The effects of untreated bednets on malaria infection and morbidity on the Kenyan coast. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2003; 97(4): 369-72.
54. Russell TL, Lwetoijera DW, Maliti D, Chipwaza B, Kihonda J, Charlwood JD, et al. Impact of promoting longer-lasting insecticide treatment of bed nets upon malaria transmission in a rural Tanzanian setting with pre-existing high coverage of untreated nets. Malaria Journal. 2010; 9 (1)(187).
55. Zaim M, Aitio A, Nakashima N. Safety of pyrethroid-treated mosquito nets. Medical & Veterinary Entomology. 2000; 14(1): 1-5.
56. Curtis V, Kanki B. Bednets and malaria. Afr Health. 1998; 20(4): 22-3.
57. Brown M, Hebert AA. Insect repellents: An overview. J Am AcadDermatol. 1997; 36(2): 243-9.
58. Faulde MK, Albiez G, Nehring O. Insecticidal, acaricidal and repellent effects of DEET- and IR3535-impregnated bed nets using a novel long-lasting polymer-coating technique. Parasitol Res. 2010; 106(4): 957-65.
59. Moore SJ, Darling ST, Sihuincha M, Padilla N, Devine GJ. A low-cost repellent for malaria vectors in the Americas: results of two field trials in Guatemala and Peru. Malaria Journal. 2007; 6.
60. N'Guessan R, Rowland M, Moumouni TL, Kesse NB, Carnevale P. Evaluation of synthetic repellents on mosquito nets in experimental huts against insecticide-resistant Anopheles gambiae and Culexquinquefasciatus mosquitoes. Trans R Soc Trop Med Hyg. 2006; 100(12): 1091-7.
61. Ahorlu C, Koram K. Intermittent preventive treatment for children (IPTC) combined with timely home treatment for malaria control. Malaria Journal. 2012; 11(Suppl 1): P108.
62. Ahorlu C, Koram K, Seakey A, Weiss M. Effectiveness of combined intermittent preventive treatment for children and timely home treatment for malaria control. Malaria Journal. 2009; 8(1): 292.
63. Nakibuuka V, Ndeezi G, Nakiboneka D, Ndugwa C, Tumwine J. Presumptive treatment with sulphadoxine-pyrimethamine versus weekly chloroquine for malaria prophylaxis in children with sickle cell anaemia in Uganda: a randomized controlled trial. Malaria Journal. 2009; 8(1): 237.
64. Vinetz JM, Clain J, Bounkeua V, Eastman RT, Fidock D. Chemotherapy of Malaria. In: Brunton LL, Chabner BA, Knollmann BC, editors. The pharmacological basis of therapeutics. 12 ed. New York: McGrawHill; 2011. p. 1383-418.
65. Desjardins RE, Doberstyn EB, Wernsdorfer WH. The treatment and prophylaxix of malaria. In: Wernsdorfer WH, McGregor SI, editors. Malaria principles and practice of malariology. London: Churchill Livingstone; 1988. p. 827-64.
66. Winstanley PA. Chemotherapy for Falciparum Malaria: The Armoury, the Problems and the Prospects. Parasitology Today. 2000; 16(4): 146-53.
67. Lalloo DG, Shingadia D, Pasvol G, Chiodini PL, Whitty CJ, Beeching NJ, et al. UK malaria treatment guidelines. Journal of Infection. 2007; 54(2): 111-21.
68. vanAgtmael MA, Eggelte TA, van Boxtel CJ. Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. Trends in Pharmacological Sciences. 1999; 20(5): 199-205.
69. Winstanley P, Ward S. Malaria chemotherapy. In: Molineux DH, editor. Control of human parasitic diseases. London: Academic Press; 2007. p. 47-76.
70. Abuaku B, Duah N, Quaye L, Quashie N, Koram K. Therapeutic efficacy of artemether-lumefantrine combination in the treatment of uncomplicated malaria among children under 5 years in 3 ecological zones in Ghana. Malaria Journal. 2012; 11(Suppl 1): P107.
71. Adjei G, Kurtzhals J, Rodrigues O, Alifrangis M, Hoegberg L, Kitcher E, et al. Amodiaquine-artesunatevsartemether-lumefantrine for uncomplicated malaria in Ghanaian children: a randomized efficacy and safety trial with one year follow-up. Malaria Journal. 2008; 7(1): 127.
72. Ayede I, Falade A, Sowunmi A, Jansen F. An open randomized clinical trial in comparing two artesunate-based combination treatments on Plasmodium falciparum malaria in Nigerian children: artesunate/ sulphamethoxypyrazine/ pyrimethamine (fixed dose over 24 hours) versus artesunate/amodiaquine (fixed dose over 48 hours). Malaria Journal. 2010; 9(1): 378.
73. Betson M, Sousa-Figueiredo J, Clifford S, Atuhaire A, Arinaitwe M, Adriko M, et al. Artemther-

lumefantrine is partially effective for treating chronic multi-species malaria in Ugandan pre-school children. Malaria Journal. 2012; 11(Suppl 1): P11.

74. WHO. Guidlines for the treatment of malaria. WHO/HTM/MAL/20061108. 2006.
75. Bougouma E, Tiono A, Ouedraogo A, Soulama I, Diarra A, Yaro J-B, et al. Haemoglobin variants and Plasmodium falciparum malaria in children under five years of age living in a high and seasonal malaria transmission area of Burkina Faso. Malaria Journal. 2012; 11(1): 154.
76. Feachem RGA. Shrinking the Malaria Map, A Guide on Malaria Elimination for Policy Makers. San Francisco The Global Health Group; 2009.
77. Walther B, Miles D, Crozier S, Waight P, Palmero M, Ojuola O, et al. Placental Malaria is associated with reduced early life weight development of affected children independent of low birth weight. Malaria Journal. 2010; 9(1): 16.
78. Dubovsky F, Rabinovich NR. Malaria vaccines. In: Plotkin SA, Orenstein WA, editors. Vaccines. Philadelphia: Saunders; 2004. p. 1283-9.
79. Good MF. towards a blood-stage vaccine for malaria: are we following all the leads? Nature Reviews Immunology. 2001; 1: 117-25.
80. Sutherland C. A Challenge for the Development of Malaria Vaccines: Polymorphic Target Antigens. PLoS Medicine. 2007; 4(3): 0413-4.
81. Carter R. Transmission blocking malaria vaccines. Vaccine. 2001; 19(17-19): 2309-14.
82. Herrera S, Corradin G, Arévalo-Herrera M. An update on the search for a Plasmodium vivax vaccine. Trends in Parasitology. 2007; 23(3): 122-8.
83. Leach A, Vekemans J, Lievens M, Ofori-Anyinam O, Cahill C, Owusu-Agyei S, et al. Design of a phase III multicenter trial to evaluate the efficacy of the RTS,S/AS01 malaria vaccine in children across diverse transmission settings in Africa. Malaria Journal. 2011; 10(1): 224.
84. Lievens M, Aponte J, Williamson J, Mmbando B, Mohamed A, Bejon P, et al. Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS,S/AS01 malaria vaccine in African children. Malaria Journal. 2011; 10(1): 222.
85. Feachem RGA, Phillips AA, Targett GA. Shrinking the Malaria Map, A Prospectus on Malaria Elimination. San Francisco The Global Health Group; 2009.
86. Narasimhan V, Attaran A. Roll back malaria? The scarcity of international aid for malaria control. Malar J. 2003; 2(8): 15.
87. WHO. The Abuja declaration, The African Summit on Roll Back Malaria. WHO/CDS/RBM/200346. 2003.
88. UN. Millennium Development Goals: UN; 2000.
89. Moonasar D, Nuthulaganti T, Kruger PS, Mabuza A, Rasiswi ES, Benson FG, et al. Malaria control in South Africa 2000-2010: beyond MDG6. Malar J. 2012; 11(294): 1475-2875.
90. Achan J, Kakuru A, Ikilezi G, Ruel T, Clark TD, Nsanzabana C, et al. Antiretroviral agents and prevention of malaria in HIV-infected Ugandan children. N Engl J Med. 2012; 367(22): 2110-8.
91. WHO. The Global Malaria Action Plan. Geneva: WHO; 2008.
92. Hemingway J, Beaty BJ, Rowland M, Scott TW, Sharp BL. The Innovative Vector Control Consortium: improved control of mosquito-borne diseases. Trends in Parasitology. 2006; 22(7): 308-12.
93. Wernsdorfer WH, Payne D. Ditesrug Sensitivity tests in Malaria Paras. In: Wernsdorfer WH, McGregor SI, editors. Malaria Principles and Practice of Malariology. New York: Churcill Livingstone; 1988. p. 1765-800.
94. Mbugi E, Mutayoba B, Malisa A, Balthazary S, Nyambo T, Mshinda H. Drug resistance to sulphadoxine-pyrimethamine in Plasmodium falciparum malaria in Mlimba, Tanzania. Malaria Journal. 2006; 5(1): 94.
95. Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM, et al. Evidence of Artemisinin-Resistant Malaria in Western Cambodia. N Engl J Med. 2008; 359(24): 2619-20.
96. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med. 2009; 361(5): 455-67.
97. Enayati AA, Ranson H, Hemingway J. Insect glutathione transferases and insecticide resistance. Insect Mol Biol. 2005; 14(1): 3-8.
98. Enayati AA, Vatandoost H, Ladonni H, Townson H, Hemingway J. Molecular evidence for a kdr-like pyrethroid resistance mechanism in the malaria vector mosquito Anophelesstephensi. Medical and Veterinary Entomology. 2003; 17: 138–44.
99. Darriet F, Guillet P, N'Guessan R, Doannio JM, Koffi A, Konan LY, et al. Impact of resistance of Anopheles gambiaes.s. to permethrin and deltamethrin on the efficacy of impregnated mosquito nets. Medicine Tropicale. 1998; 58(4): 349-54.
100. Darriet F, N'guessan R, Koffi AA, Konan L, Doannio JM, Chandre F, et al. Impact of pyrethrin resistance on the efficacity of impregnated mosquito

nets in the prevention of malaria: results of tests in experimental cases with deltamethrin SC. Bull SocPatholExot. 2000; 93(2): 131-4.

101. N'Guessan R, Darriet F, Doannio JM, Chandre F, Carnevale P. Olyset Net efficacy against pyrethroid-resistant Anopheles gambiae and Culexquinquefasciatus after 3 years' field use in C te d'Ivoire. Med Vet Entomol. 2001; 15(1): 97-104.
102. N'Guessan R, Corbel V, Akogbéto M, Rowland M. Reduced efficacy of insecticide-treated nets and indoor residual spraying for malaria control in pyrethroid resistance area, Benin. Emerging Infectious Diseases. 2007; 13(2): 199-206.
103. Chandre F, Darriet F, Duchon S, Finot L, Manguin S, Carnevale P, et al. Modifications of pyrethroid effects associated with kdr mutation in Anopheles gambiae. Med Vet Entomol. 2000; 14(1): 81-8.
104. Chouaibou M, Simard F, Chandre F, Etang J, Darriet F, Hougard JM. Efficacy of bifenthrin-impregnated bednets against Anopheles funestus and pyrethroid-resistant Anopheles gambiae in North Cameroon. Malaria Journal. 2006; 11(5): 77.
105. Dabiré RK, Diabaté A, Baldet T, Paré-Toé L, Guiguemdé RT, Ouédraogo JB, et al. Personal protection of long lasting insecticide-treated nets in areas of Anopheles gambiaes.s. resistance to pyrethroids. Malaria Journal. 2006; 5(12): 8.
106. Doannio JM, Dossou-Yovo J, Diarrassouba S, Chauvancy G, Darriet F, Chandre F, et al. Efficacy of permethrin-impregnated Olyset Net mosquito nets in a zone with pyrethroid resistant vectors. I--Entomologic evaluation. Medicine Tropicale. 1999; 59(4): 349-54.
107. Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Annals of Tropical Medicine & Parasitology. 2001; 95(8): 741- 54.
108. Nájera JA. Malaria control among refugees and displaced populations: WHO; 1996.
109. Anderson J, Doocy S, Haskew C, Spiegel P, Moss WJ. The burden of malaria in post-emergency refugee sites: A retrospective study. Confl Health. 2011; 5(1): 1752-505.
110. Watson JT, Gayer M, Connolly MA. Epidemics after natural disasters. Emerg Infect Dis. 2007; 13(1): 1-5.
111. Deribew A, Birhanu Z, Sena L, Dejene T, Reda A, Sudhakar M, et al. The effect of household heads training about the use of treated bed nets on the burden of malaria and anaemia in under-five children: a cluster randomized trial in Ethiopia. Malaria Journal. 2012; 11(1): 8.
112. Bingham A, Gaspar F, Lancaster K, Conjera J, Collymore Y, Ba-Nguz A. Community perceptions of malaria and vaccines in two districts of Mozambique. Malar J. 2012; 11(1): 394.
113. Ahmed S, Haque R, Haque U, Hossain A. Knowledge on the transmission, prevention and treatment of malaria among two endemic populations of Bangladesh and their health-seeking behaviour. Malaria Journal. 2009; 8(1): 173.
114. de Castro M, Fisher M. Is malaria illness among young children a cause or a consequence of low socioeconomic status? evidence from the united Republic of Tanzania. Malaria Journal. 2012; 11(1): 161.
115. Krefis A, Schwarz N, Nkrumah B, Acquah S, Loag W, Sarpong N, et al. Principal component analysis of socioeconomic factors and their association with malaria in children from the Ashanti Region, Ghana. Malaria Journal. 2010; 9(1): 201.
116. Kisia J, Nelima F, Otieno D, Kiilu K, Emmanuel W, Sohani S, et al. Factors associated with utilization of community health workers in improving access to malaria treatment among children in Kenya. Malaria Journal. 2012; 11(1): 248.
117. Coldren RL, Prosser T, Ogolla F, Ofula VO, Adungo N. Literacy and recent history of diarrhoeaare predictive of Plasmodium falciparum parasitaemia in Kenyan adults. Malar J. 2006; 5: 96.