



## Malaria in Children, Prospects and Challenges

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### 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 been several 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.<sup>1, 2</sup> 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.<sup>1, 3</sup> 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.<sup>4</sup> The disease may cause as many as 10% of all deaths in children.<sup>1</sup>

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## Burden of Malaria

In 1900, more than 77% of the world population in 140 countries were at risk of malaria<sup>5</sup> 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<sup>6</sup>, though this statistics dramatically reduced to 1.61 per 10,000 by 1970.<sup>7</sup>

According to the World Malaria Report published in 2011, there were 655,000 malaria deaths worldwide in 2010, compared to 781,000 in 2009.<sup>1</sup> 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.<sup>1</sup> 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.<sup>2</sup>

## Malaria in Iran

There are eight Anopheles species transmitting the disease in Iran the most important of which are An. stephensi and An. culicifaciens. The most frequent parasites are P. Vivax and P. Falciparum leaving the third species, P. Malaria, consisting only 3-4%.<sup>8</sup> 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.<sup>8</sup> 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.<sup>9</sup> The total number of confirmed cases in 2010 was 3031 of which 1847 were locally acquired and 1184 were imported cases.<sup>1</sup> Iran moved to the elimination

stage in 2010, and adopted a nation-wide elimination strategy in that year.<sup>1</sup>

## Malaria in Mazandaran

Malaria in Mazandaran is under control since the end of the GMEC in 1967.<sup>8, 10</sup> 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.<sup>10</sup>

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.<sup>8</sup>

## Malaria transmission

### Mosquito bite

The disease is exclusively transmitted through the bite of female Anopheles mosquitoes that occurs between dusk and dawn. 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.<sup>11</sup> After one exoerythrocytic and a few cycles of erythrocytic schizogony, 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.<sup>12, 13</sup>

### 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<sup>14</sup>. 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.<sup>12</sup>

### 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.<sup>4, 15</sup>

### 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.<sup>16</sup>

### Other routes of malaria transmission

Malaria also can be transmitted through the use of contaminated needles.<sup>4, 17</sup> Organ transplantation is another malarial transmission route.<sup>18</sup>

### 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. malariae* predominate in Southeast Asia, South America, and Oceania, *P. ovale* and *P. knowlesi* (the least common species) are transmitted primarily in Africa.<sup>19,4</sup> Most malaria cases acquired in Africa are due to *P. falciparum*. *P. vivax* dominates in Asia and the Americas.<sup>1</sup>

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.<sup>8</sup>

### 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.<sup>4</sup> Splenomegaly, 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.<sup>4</sup>

The periodicity of malarial fever and other symptoms depends on the time required for the erythrocyticshizogony and 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.<sup>12</sup> 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.<sup>4</sup> The criteria in children emphasize more on consciousness, severe anemia, and respiratory distress.<sup>20</sup> 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.<sup>21</sup>

## 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.<sup>12, 22</sup> 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.<sup>4</sup>

### Polymerase Chain Reaction

Although morphologically distinguishable, PCR strategies have been developed to diagnose *P. falciparum* and *P. vivax*<sup>23</sup>. However, *P. knowlesi* and *P. malariae* cannot be diagnosed morphologically, therefore, polymerase chain reaction may be helpful.<sup>4, 24</sup>

### 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.<sup>25-27</sup>

### 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.<sup>28</sup>

### 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 Myelocytic Leukemia, leptospirosis, tuberculosis, relapsing fever, typhoid fever and yellow fever.<sup>25, 28, 4</sup> 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.<sup>25</sup>

### Complications of malaria in children

The most common complications in children are severe anemia.<sup>29,30</sup> impaired consciousness (including cerebral malaria)<sup>31</sup>, respiratory

distress (due to metabolic acidosis)<sup>32, 33</sup>, multiple seizures<sup>34-36</sup>, Black Water Fever and jaundice<sup>37</sup> leading to poor prognosis.<sup>38,39</sup> 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.<sup>40, 414</sup>

## Malaria management

Malaria can be prevented and once contracted should be treated<sup>1</sup> 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.<sup>42</sup>

### Vector Control

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

#### 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.<sup>43,42, 44</sup>

Application of non-residual formulations like aerosols in houses especially children's bedrooms before retiring at night is also recommended for temporary malaria control.<sup>45, 46</sup> 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,<sup>11, 47-54</sup> but ITNs are far more effective than untreated nets in reducing malaria especially in children less than 5 years of age.<sup>47</sup> 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.<sup>55</sup>

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.<sup>56</sup>

### 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.<sup>57-60</sup>

### Chemoprophylaxis and intermittent presumptive therapy

Chemoprophylaxis and intermittent presumptive therapy (IPT) are available to control malaria.<sup>61-63</sup> 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.<sup>3</sup> The drugs used for the chemoprophylaxis of malaria are given in Table 1.<sup>64</sup>

### Treatment

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

blood schizontocidal effects e.g. chloroquine and amodiaquine, and primaquine with gametocidal effect as well as activity against hypnozoites.<sup>40, 65-67</sup>

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

### **Malaria treatment in Iran**

Based on the WHO recommended treatment for malaria, Iranian Centers for Disease Control and Prevention (CDC) issues and updates guidelines for malaria treatment is summarized in Table 2. Information is given for pediatric 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.<sup>75</sup> 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.<sup>4</sup> 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.<sup>3, 76</sup> 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.<sup>77</sup> As vulnerable groups, young children (under 5 years) and pregnant women should be at the centre of malaria control programmes in highly endemic areas.<sup>3</sup>

### **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<sup>78</sup>, 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<sup>78-80</sup>, c) Transmission-blocking vaccines which prevent from the sexual stage of the parasite<sup>81</sup> and d) Anti *P. vivax* malaria vaccine with only two vaccine candidates being tested in preliminary clinical trials.<sup>82</sup>

The 1<sup>st</sup> 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.<sup>4, 83, 84</sup>

### **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.<sup>85, 86</sup> 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.<sup>86, 87</sup> Although this was an enthusiastic programme, in practice adequate resources has not gone through the plan of action, therefore the goals were never achieved.<sup>86</sup>

### **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.<sup>88, 89</sup> Management of other diseases such as HIV by providing NNRT drugs reduced the incidence and recurrence of malaria.<sup>90</sup> Based on WHO world malaria report in 2011, there were 655 000 malaria deaths worldwide in 2010, compared to 7,81,000 in 2009.<sup>1</sup> However in a recent research it was revealed that 1.24 million people died from malaria in 2010.<sup>2</sup>

### **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.<sup>91</sup>

### **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.<sup>92</sup>

### **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.<sup>1</sup>

### **Challenges Facing Malaria Control** **Drug resistance**

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

### **Insecticide resistance**

The phenomenon is caused by several different mechanisms including biochemical or site insensitivity<sup>11, 42</sup> through producing qualitatively or quantitatively different enzymes that detoxify insecticide molecules<sup>97</sup> or changes in the receptors of insecticide molecules so that they are no longer susceptible to them.<sup>98</sup> 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.<sup>48, 99-106</sup>

### **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.<sup>107-109</sup>

### **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.<sup>107-109</sup>

### **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.<sup>8</sup>

### **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.<sup>107, 110</sup>

### **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.<sup>111</sup> Though behaviors like feeling obliged for receiving health care such as vaccine may pave the way for implementing one when available.<sup>112</sup>

### **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.<sup>112</sup> Another problem is gradual transition from free healthcare to more private sector healthcare which seeks community partnership. Poverty is another issue<sup>113-115</sup> and most communities resist this privatization by not acquisition of the care owing to their economic status.<sup>116</sup> Literacy level is a major determinant in seeking healthcare.<sup>117</sup>

### **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: 3/4 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.
Hydroxychlor oquine sulfate (PLAQUENIL )	An alternative to chloroquine for prophylaxis only in areas with chloroquinesensit ivemalaria	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: 1/4 tablet once/week; >19-30 kg: 1/2 tablet once/week; >31-45 kg: 3/4 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 not normally enter houses protected by IRS or LLINs. The situation particularly in India, with 54 million population involved, in Vietnam

in 16 out of 64 provinces, in Belém, Pará, a forest fringe area of Brazil, in the forested areas of equatorial Africa, in Thailand, Cambodia, and Vietnam is now a major problem.<sup>11</sup>

**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 20<sup>th</sup> century. Major successes were in the sanitation period in the middle of the 20<sup>th</sup> 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.

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