Malaria in Children: Updates on Management and Prevention

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Malaria, the most important parasitic disease of man, is transmitted by the bite of female *Anopheles* mosquitoes and is caused by *Plasmodium falciparum*, *P. vivax*, *P. ovale wallikeri*, *P. ovale curtisi*, *P. malariae* and the zoonotic *P. knowlesi*. Approximately half the global population resides in malaria-endemic regions. An estimated 241 million cases of malaria and 627,000 deaths occurred globally in 2020.[1] More than half of the malaria deaths annually are in children younger than 5 years, their vast majority caused by *P. falciparum* in sub-Saharan Africa. *P. falciparum* is the most prevalent malaria parasite in all areas except the Americas; *P. vivax* is now recognized as the predominant cause of malaria in children and infants in the Asia-Pacific region and the Americas, with significant morbidity and mortality.[2,3] In non-endemic areas, malaria occurs mainly in returning travelers, an increasing proportion of immigrants and refugees, and people visiting friends and relatives in endemic regions. Children constitute 15%–20% of imported malaria cases worldwide.

CLINICAL PRESENTATION

Two disease presentations are described, uncomplicated or severe. Uncomplicated malaria presents nonspecifically with fever, chills, headache, myalgias, cough, vomiting and diarrhea, thus making clinical diagnosis unreliable. A high index of suspicion in all travelers to endemic areas presenting with fever is crucial for establishing the diagnosis, which is accomplished by laboratory testing. Malaria should be suspected in any child with fever, with a history of travel to a malaria-endemic country up to 1 year after return.

Severe malaria is caused primarily by *P. falciparum* and sometimes by *P. vivax* and *P. knowlesi*, the latter 2 mostly in endemic countries, not returning travelers. The most common manifestations of severe malaria in children are cerebral malaria, severe anemia, metabolic acidosis, and hypoglycemia, whereas jaundice, renal failure, and acute pulmonary edema are unusual. Cerebral malaria is a leading cause of childhood neurodisability in highly endemic areas, like sub-Saharan Africa, where surviving children are at increased risk of neurological and cognitive deficits, behavioral difficulties, and epilepsy.[4]

Malaria diagnosis is established by the detection of parasites in peripheral blood by microscopy, rapid diagnostic tests and molecular methods. Parasitological diagnosis ensures appropriate treatment and, if negative, points clinicians towards alternative diagnoses, particularly in endemic settings. Prompt same-day diagnosis is crucial, as progression to severe malaria may be rapid, particularly in children <5 years old.

MANAGEMENT

Factors guiding treatment include infecting *Plasmodium* species, geographical area of malaria acquisition, patient clinical status, and previous use of antimalarial prophylaxis, while choice of drugs depends on national policy and local availability. Preferably, treatment should not begin until laboratory testing has confirmed malaria diagnosis, although this is not always feasible. As progression to severe malaria may be rapid, it is advisable that all children suspected or diagnosed with falciparum malaria be admitted to the hospital for at least 24 hours.

UNCOMPLICATED MALARIA

The treatment objectives are to clear blood-stage infections for all *Plasmodium* species, using schizontocidal drugs, and to clear liver-stage infection for *P. vivax* and *P. ovale* using hypnozoitocidal drugs, to prevent relapse. For uncomplicated *P. falciparum*

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malaria, a 3-day course of artemisinin-based combination therapies is recommended for children and adults.[5–7] Alternative treatments include atovaquone-proguanil and quinine sulfate plus doxycycline/clindamycin. Artemisinin-based combination therapies are highly effective against all species and are increasingly used to treat all uncomplicated infections, allowing the simplification of malaria treatment. For *P. vivax* and *P. ovale* infections (or mixed infections in which these species cannot be reliably excluded), follow-up treatment with primaquine for 14 days is recommended in infants older than 6 months, to prevent relapse. Screening for G6PD deficiency should precede primaquine administration and a pediatric infectious diseases specialist consulted, if the patient is G6PD deficient.[8]

Primaquine is the only antimalarial with efficacy against all life-cycle stages, including mature gametocytes, the form of the parasite that is infective to mosquitoes. Administration of a single dose of primaquine (0.25 mg/kg) as a *P. falciparum* gametocide is recommended in low transmission settings but would also be beneficial in malaria non-endemic areas with *Anopheles* mosquitoes, where imported cases may lead to small local outbreaks.[5] In this case, knowledge of the patient's G6PD status is not necessary, as this dose, although effectively gametocidal, is not enough to cause toxicity in patients with any of the G6PD variants.[5]

SEVERE MALARIA

Severe malaria is a medical emergency, as death may occur within a few hours of hospital admission. Initial management includes respiratory, circulatory and neurological assessment and measurement of glucose, hemoglobin, and parasitemia. Cerebral malaria must be differentiated from other causes of coma, like malaria-associated hypoglycemia and bacterial meningitis. If severe malaria is strongly suspected but laboratory diagnosis is not available, blood should be collected for testing at a later time and antimalarial treatment promptly initiated. Regardless of infecting species, the recommended treatment of choice for severe malaria is parenteral artesunate.[6,7] All children treated with IV artesunate should be monitored weekly for signs of hemolytic anemia.

PREVENTION

Endemic Areas

Prevention in malaria-endemic areas comprises vector control measures, chemoprevention of populations at high risk of severe disease to treat existing and prevent new cases, and as of 2021, vaccination of children against *P. falciparum*.

For vector control in areas with ongoing malaria transmission, WHO recommends using Insecticide Treated Nets or Indoor Residual Spraying and larval control, achieved mainly via the management of water bodies.[5] Chemoprevention regimens include (1) intermittent preventive treatment of pregnant women with sulfadoxine-pyrimethamine (SP), (2) perennial chemoprevention of infants and children with SP, and (3) seasonal chemoprevention of children at high risk of severe malaria with SP plus amodiaquine. Problems in healthcare infrastructure and drug delivery systems, vector resistance to insecticides (i.e., pyrethroids), and emerging resistance of *Plasmodium* spp to antimalarials hamper malaria control efforts in endemic areas.

Following 4 decades of research and clinical trials, a 4-dose schedule of the RTS,S malaria vaccine (Mosquirix) is currently recommended for the prevention of *P. falciparum* malaria in children older than 5 months, living in regions with moderate to high transmission.[5] The vaccine contains *P. falciparum* circumsporozoite protein, fused with the HBV surface antigen, and according to WHO, could reduce severe disease in 30% of children.[9] Follow-up indicates that protection is short-lived and dependent on transmission intensity. As the vaccine does not provide sterile or anti-gametocyte immunity, patients remain infected by mosquitoes; therefore, it does not affect transmission and endemicity.[9] Studies indicate an increase in rebound episodes of malaria in children vaccinated and protected by immunization with RTS,S after 3–6 years, possibly due to decreased immune response of vaccinees to parasitic blood stages. Thus it is increasingly believed that although pre-erythrocytic stage vaccines are an important first step, immunization should also induce anti-blood stage immune responses.[9]

TRAVELERS

For travelers to endemic areas, malaria prevention is guided by the ABCDE principles.[10] (1) Awareness: travelers should be informed about malaria risk at their destination. (2) Bite prevention: protection from mosquito bites between dusk and dawn is accomplished by sleeping under mosquito bed nets, application of insect repellents to the skin, preferably those containing DEET ≥30%, and use of protective clothing. (3) Chemoprophylaxis: atovaquone/proguanil, mefloquine, and doxycycline are most commonly used (Table 1). No antimalarial drug is 100% protective. (4) Diagnosis and prompt treatment: travelers should be aware of malaria symptoms, for which they should seek medical assistance and remain vigilant for up to 1 year after their return from endemic areas. (5) Emergency treatment: travelers are encouraged to carry a full course of antimalarial treatment to be used in case of infection.[10]

FUTURE CHALLENGES

Parasite resistance to antimalarials and vector resistance to insecticides continue to hinder the progress of malaria control programs. Artemisinin resistance in *P. falciparum* is currently prevalent in parts of Southeast Asia, where piperaquine and mefloquine resistance also occur. The loss of first-line drugs has prompted considerations of using triple combinations for malaria treatment, while underlining the need for new antimalarials.[2] Thirteen new antimalarial drugs are currently in clinical development, including artefenomel, arterolane, and 2 artemisinin unrelated compounds, cipargamin and ganaplacide, to be used as part of new combinations.[2] The extensive use of long-lasting insecticidal nets was accompanied by the emergence of vector resistance to pyrethroids. Combining 2 or more compounds of different insecticide classes into a single formulation is a possible approach to combating resistance; results of a clinical trial for a new chlorfenapyr-impregnated long-lasting insecticidal net have recently been published.[11]

RTS,S is the first malaria vaccine to have obtained regulatory approval. The historic decision was received with cautious optimism, as it can have a substantial impact in terms of lives saved and episodes of malaria averted; however, how this vaccine will fit into malaria control programs remains unclear. Most malariologists believe that although pre-erythrocytic stage vaccines like RTS,S are a significant first step in the right direction, the highest impact on infection, morbidity, and transmission of malaria would be achieved by a multi-stage vaccine, inducing anti-sporozoite and anti-blood stage immune responses.[9] Additional candidate vaccines are currently in various stages of development.

The first milestone toward malaria elimination—to achieve a 40% global reduction in malaria mortality rate and case incidence by 2020, was missed; in fact, the last 2 World Malaria Reports recorded an increase in cases and malaria deaths after 2019.[1] WHO warned that global targets of reducing malaria case incidence and mortality rates by at least 90% by 2030 would also be missed.[12] The setbacks in malaria control programs were a concern even before the Covid-19 pandemic overwhelmed health systems worldwide. Continued diversion of resources due to COVID-19 could—in a worst-case

TABLE 1. Chemoprophylaxis for Malaria in Travelers

	Drugs	Adults	Children	Regimen	Comments
Areas of chloroquine-resistant *P. falciparum*	Atovaquone/ Proguanil (Malarone)	250/100 mg 1 tab	4/1.6 mg/kg daily 5–7 kg ½ ped tab 8–9 kg ¾ ped tab 10–19 kg 1 ped tab 20–29 kg 2 ped tab 30–39 kg 3 ped tab >40 kg 1 adult tab	Daily 1–2 days before departure until 7 days after return	Not recommended in children <5 kg
	Mefloquine	250 mg base 1 tab	5 mg base/kg/weekly 6–9 kg ¼ tab 10–15 kg ¼ tab 16–24 kg ½ tab 25–44 kg ¾ tab >45 kg 1 tab	Weekly 2–3 weeks before departure until 4 weeks after return	*P. falciparum* resistance to mefloquine encountered in some areas of South-east Asia, reported sporadically from the Amazon basin. Not recommended in children <5 kg
	Doxycycline	100 mg 1 tab	1.5 mg/kg daily 25–44 kg 1 tab (from age > 12 years) >45 kg 1 tab	Daily 1–2 days before departure until 4 weeks after return	Contraindicated <12 years Not recommended <25 kg
Areas of little chloroquine resistance	Chloroquine	300 mg base 2 tab	5 mg base/kg weekly <6 kg ¼ tab 6–9 kg ½ tab 10–15 kg ¾ tab 16–24 kg 1 tab 25–44 kg 1 ½ tab >45 kg 2 tab	Weekly 1 week before departure until 4 weeks after return	Can be co-administered with proguanil Not to be used in those with history of epilepsy May exacerbate psoriasis and myasthenia gravis.
	Proguanil	100 mg 2 tab	<6 kg ¼ tab 6–9 kg ½ tab 10–15 kg ¾ tab 16–24 kg 1 tab 25–44 kg 1 ½ tab >45 kg 2 tab	Daily 1 week before departure until 4 weeks after return	To be taken orally with food Antacids and adsorbents may reduce absorption

Adapted from Reference 10.

scenario - lead to a resurgence of malaria, putting hundreds of thousands of lives at stake. Even with the new vaccine, malaria eradication remains a distant goal; the case for a global commitment to health systems strengthening, funding, and global collaboration is, therefore, quite strong.

REFERENCES

1. World Malaria Report 2021. Available at: https://www.who.int/teams/global-malaria-programme/reports. Accessed July 31, 2022.
2. Ashley EA, Poespoprodjo JR. Treatment and prevention of malaria in children. *Lancet Child Adolesc Health*. 2020 Oct;4:775–789.
3. Battle KE, Lucas TCD, Nguyen M, et al. Mapping the global endemicity and clinical burden of Plasmodium vivax, 2000-17: a spatial and temporal modelling study. *Lancet*. 2019;394:332–343.
4. Idro R, Marsh K, John CC, et al. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. *Pediatr Res*. 2010;68:267–274.
5. WHO Guidelines for malaria, 3 June 2022. Geneva: World Health Organization. 2022. (WHO/UCN/GMP/2022.01 Rev.2). Available at https://apps.who.int/iris/handle/10665/354781. Accessed August 1, 2022.
6. Lalloo DG, Shingadia D, Bell DJ, et al. PHE advisory committee on malaria prevention in UK travellers. UK malaria treatment guidelines 2016. *J Infect*. 2016;72:635–649.
7. Centers for Disease Control and Prevention. Global Health, Division of Parasitic Diseases and Malaria. Malaria Treatment (United States). Available at https://www.cdc.gov/malaria/diagnosis_treatment/index.html. Accessed August 1, 2022.
8. Kiang KM, Bryant PA, Shingadia D, et al. The treatment of imported malaria in children: an update. *Arch Dis Child Educ Pract Ed*. 2013;98:7–15.
9. Zavala F. RTS, S: the first malaria vaccine. *J Clin Invest*. 2022;132:e156588.
10. Guidelines for malaria prevention in travellers from the UK. 2021. Available at https://www.gov.uk/government/publications/malaria-prevention-guidelines-for-travellers-from-the-uk. Accessed August 1, 2022.
11. Kariuki S, Kamau L. A new generation of long-lasting insecticidal nets. *Lancet*. 2022;399:1202–1203.
12. The L. Malaria in 2022: a year of opportunity. *Lancet*. 2022;399:1573.