Prevention of Malaria in Children

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Although malaria kills ~1 million children each year and is also a major cause of illness, health care visits, and hospitalizations in many areas of the world [1]. Although 2.4 billion people on the planet live under the threat of malaria, most of the morbidity and mortality with the disease is seen in sub-Saharan Africa [2, 3]. Like residents of regions where malaria is endemic, children traveling in such areas are also at risk. Each year, ~1000 cases of malaria are imported into the United States [4] and ~7000 are imported into Europe [5]; cases in children are well documented [6, 7] and comprise 5%–10% of imported cases in some unpublished reports.

Worldwide efforts to combat malaria have moved from the unsuccessful eradication attempts of the 1950s through the control efforts of the 1980s to the current Roll Back Malaria program (http://www.rbm.who.int) [8]. Spurred by widespread publicity and fueled by newly mobilized resources, current control efforts have increased the optimism that malaria can be subdued. However, what can be done now to prevent malaria in children? Specific interventions are possible to avoid malaria infection, to prevent malaria illness, and to preempt malaria-associated mortality. These measures are easily implemented for children whose families have the resources to travel to areas where malaria is endemic, and similar efforts, when affordable, could benefit young residents of these regions.

AVOIDING MALARIA INFECTION

The majority of cases of malaria are acquired via a bite from an infected mosquito, although some cases are acquired transplacentally or via transfusion of blood products. Generally, to avoid malaria infection, a child must avoid being bitten by an infected mosquito. This can be accomplished by choosing appropriate times and places for activities, controlling the physical environment, blocking mosquitoes’ access to the skin, repelling mosquitoes from the skin, and killing mosquitoes near the child. Table 1 outlines practical advice about mosquito avoidance for traveling children.

Malaria is transmitted by female anopheline mosquitoes, which bite either outdoors or indoors during evening and night hours. Thus, a child should spend the evening and night hours in a mosquito-free environment, such as inside a house with screened windows and closed doors. When they are in areas of endemicity, travelers should schedule activities so that children are not outside during evening hours, when anopheline mosquitoes are most likely to bite. In some areas, malaria transmission is seasonal, and elective trips could be planned for the dry season, when transmission is less common.

Mosquitoes spend their lives in and around standing water. Human living areas should be free of persistent puddles and open water-containers. In some areas, small fish that feed on insect larvae are kept in fountains and water storage containers as a means of mosquito control [9].

Given that mosquitoes and children do end up sharing the same living areas, physical barriers should be used to block the access of mosquitoes to children’s skin. Skin should be covered with clothing (lightweight for comfort and light-colored to be
Table 1. Practical advice for avoiding malaria infection.

<table>
<thead>
<tr>
<th>Proactive protective actions</th>
<th>Protective actions in area of endemicity</th>
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<tbody>
<tr>
<td>Schedule a visit to an area where malaria is endemic during seasons of low transmission</td>
<td>Eliminate standing water near housing</td>
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<tr>
<td>Plan to spend evenings and nights in closed buildings</td>
<td>Cover skin with long-sleeved shirt and long pants or dress</td>
</tr>
<tr>
<td>Impregnate clothes and bed nets with insecticide</td>
<td>Use bed nets</td>
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<tr>
<td></td>
<td>Apply concentrated DEET to skin, avoiding oral and ocular contamination</td>
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NOTE: DEET, N,N-diethyl m-toluamide or N,N-diethyl-3-methylbenzamide.

less attractive to insects). Sleeping children should be surrounded by bed nets. Nets to fit various sizes and styles of beds are available through the Internet, for example at the Travel Medicine Web site (http://www.travmed.com).

Clothes and bed nets can be impregnated with an insecticide to increase their effectiveness in protecting children. Products such as 0.5% permethrin can be sprayed on clothes and nets to moisten them; the material should then be allowed to air dry for at least 6 h before use. Even if laundered, the impregnated clothes will remain insecticidal for 2–6 weeks [10]. Impregnated nets seem to retain their protective ability for 6–12 months and have been shown to decrease overall malaria mortality and morbidity in communities [11].

Applied topically to skin, chemical repellents are effective in reducing the number of mosquito bites received. DEET (N,N-diethyl m-toluamide or N,N-diethyl-3-methylbenzamide) is the gold standard; it has proven its safety and effectiveness for >40 years [12, 13]. Nonetheless, 13 serious adverse neurologic events have occurred concurrent with DEET use. Details of these cases were not fully recorded, but at least some were related to oral ingestion or overapplication of DEET [14]. Despite myths to the contrary, high concentrations of DEET have not been linked to adverse effects, but higher concentrations have longer durations of effectiveness [15]. Children can safely apply DEET in concentrations of ≥30%, which will provide 4–6 h of repellent activity. Use of newer formulations of DEET (such as those incorporating DEET into liposomes) extends the duration of protection to 12 h. DEET in any form is toxic if ingested orally, and ocular contact will irritate the eyes and should be avoided. Therefore, DEET should not be applied to the hands, forearms, or faces of young children. DEET-containing repellents can interact with concurrently applied sunscreens to limit sunscreen effectiveness by 34% [16], but the insect-repellent efficacy of DEET is unchanged by concurrent sunscreen use [17].

No insect repellent has yet been identified that is more effective than DEET [12]. “Natural” products that contain citronella have only a short-term (~30 min) effect in repelling mosquitoes. Some perfumed repellents might actually attract mosquitoes. A new topical insect repellent, 1-pipetidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester (trade name, Bayrepel [Bayer]), is under development, and its effectiveness is similar or superior to that of DEET in field studies. Its use is recommended by the World Health Organization [18], and it has been licensed in several countries for use on children aged >2 years. Safety studies have not yet been performed for younger children.

Environmental insecticides, such as those released by slowly burning coils, seem to decrease indoor mosquito populations by 50%–75% [19, 20], but some cases of airway irritation have been reported with the use of these products [21]. Ultrasonic buzzers and devices that electrocute insects have not been found to reduce bites from infected mosquitoes [19]. Community spraying of insecticides is expensive but effective in limiting mosquito populations.

PREVENTING MALARIA DISEASE

After the host is bitten by an infective mosquito, malaria parasites remain in the circulation for ~30 min before gaining entry into hepatocytes. There, the parasites develop for at least 1–1.5 weeks before returning to the circulatory system to infect RBCs and cause symptoms of malaria disease; some strains of species other than Plasmodium falciparum, however, can persist in the liver for months to years. Newer prophylactic medications, such as atovaquone-proguanil and primaquine, are able to kill the parasites effectively before they return from the liver to the blood system. Most chemoprophylactic agents, however, act by maintaining a concentration in the circulating blood adequate to prevent the infection from becoming established in RBCs. Thus, the infection is aborted before symptoms develop.

Chemoprophylaxis has been used effectively for decades, but the increasing resistance of Plasmodium to medications has limited the effectiveness of chemoprophylactic regimens used in the past [22]. In areas of endemicity, chemoprophylactic efforts have been hindered by cost and programmatic difficulties. Nonetheless, mosquito avoidance and chemoprophylaxis are the mainstays of malaria prevention for children traveling from areas where malaria is not endemic to areas where it is.

Figure 1 shows countries and areas where there is risk of acquiring malaria. As displayed in the figure, the selection of the appropriate antimalarial medication should be individualized according to the patterns of resistance in the geographical region where exposure is anticipated. The Web sites of the Centers for Disease Control and Prevention (http://www.cdc.gov) and the World Health Organization (http://www.who.int) give specific guidance. In general, chloroquine is the first choice for che-
moprophylaxis for children going to areas where malaria is still sensitive to chloroquine. Mefloquine is generally a good option for children traveling to areas where chloroquine-resistant malaria is prevalent; atovaquone-proguanil and (for children ≥8 years of age) doxycycline are good alternative choices. Children who must travel to areas where there is mefloquine-resistant malaria would usually receive atovaquone-proguanil or, if they are ≥8 years old, doxycycline.

Table 2 notes medications effective in chemoprophylaxis and details about recommended dosages. Clearly, the use of any preventive medication must be customized on the basis of the child’s age, size, and health. There are not good data to specify the duration of chemoprophylaxis in children, but continuous use for ≥2 years is probably safe.

Chloroquine, a 4-amo–quinolone, was once the mainstay of malaria chemoprophylaxis but has become less useful as the parasites have developed resistance to its effects. As noted on figure 1, its usefulness is limited to a few areas of Latin America, the Mideast, and Asia. Chloroquine is rapidly absorbed and becomes more concentrated in RBCs than in plasma. Approximately one-half is secreted in the urine, and the other one-half is biotransformed by the liver; metabolites are important to the prophylactic effect, and the half-life is 6–10 days [23]. Toxicity is unusual with the dosages given as prophylaxis, but pruritus is sometimes seen, especially in Africans and African-Americans. There is some concern that the cumulative doses achieved after ≥5 years of continual prophylaxis might be associated with a retinopathy and, therefore, periodic retinal examinations are sometimes recommended for children receiving long-term prophylaxis. Chloroquine is generally safe for most children. Overdosing, however, can be dangerous, and attention should be paid to pill safety and the avoidance of inadvertent ingestion of pills.

The addition of proguanil, given daily, to chloroquine, given weekly, provides an effective prophylactic regimen in some parts of the world. Nonetheless, malaria with increasing resistance to this regimen has extended to East Africa and other areas, and this combination of prophylaxis is no longer a first-line choice for chemoprophylaxis. In addition, proguanil is not licensed for use in the United States. It is generally safe for children, but transient hair loss, mouth sores, and mild gastrointestinal symptoms have been associated with its use.
Table 2. Chemoprophylactic agents for malaria.

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dosage</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Chloroquine</td>
<td>5 mg/kg weekly; maximum dose, 300 mg; begin 1 week before exposure, continue 4 weeks after exposure</td>
<td>Mostly effective in Central America</td>
</tr>
<tr>
<td>Chloroquine plus proguanil</td>
<td>Chloroquine as above; proguanil 4 mg/kg daily (or 3 mg/kg per day in 2 divided doses); maximum dose, 200 mg</td>
<td>Increasing resistance has been noted</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>5 mg/kg weekly; maximum dose, 250 mg; begin 1–2 weeks before exposure and continue 4 weeks after exposure</td>
<td>Effective in Africa, Asia, South America; no limits to the age or size of the patient; do not administer if the patient has seizures, dysrhythmia, or psychiatric problems</td>
</tr>
<tr>
<td>Atovaquone plus proguanil</td>
<td>1 pediatric pill (1/4 of an adult pill) per 10 kg daily; maximum dose, 4 pediatric pills (1 adult pill); begin 1–2 days before exposure and continue 7 days after exposure</td>
<td>Alternative to mefloquine; dosage, 250 mg atovaquone + 100 mg proguanil per adult pill</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>2 mg/kg daily, maximum 100 mg</td>
<td>Ineffective near some of the border areas of Thailand; do not administer if patient is &lt;8 years old; alternative to mefloquine</td>
</tr>
<tr>
<td>Primaquine</td>
<td>0.5 mg/kg daily; maximum dose, 30 mg</td>
<td>Not yet recommended; there is some risk if the patient’s G6PD level is low</td>
</tr>
<tr>
<td>Tafenoquine</td>
<td>Pending</td>
<td>Studies in progress; there is some risk if the patient’s G6PD level is low</td>
</tr>
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NOTE. G6PD, glucose-6-phosphate dehydrogenase.

Mefloquine, a quinoline-methanol compound, is effective against malaria in most travel destinations, with the exception of some regions near Thailand’s borders with Cambodia and Myanmar. It is rapidly absorbed, and absorption might be improved by taking it with a meal [23]. It is generally available only in tablet form and has a taste that many children do not enjoy. There are anecdotal reports that taking mefloquine after eating and administration with either a cola drink or chocolate seem helpful for some children. Emesis within 30 min of ingestion should prompt a second administration of the entire dose. Mefloquine seems to have an adverse reaction profile that is similar in children and in adults, but the exact risks for mild side effects are not well understood, especially in young children. In adults, bothersome effects (nausea, vomiting, insomnia, vivid dreams) occur in ~10%–15% of those who receive it, and serious neuropsychiatric side effects have also been reported; <5% of individuals treated need to discontinue treatment because of side effects. Comparative studies suggest that the frequency of side effects with mefloquine is similar to that with other preventive antimalarial regimens [24]. Serious adverse reactions are less likely with prophylactic than with curative dosages. Mefloquine does affect cardiac conduction and can lower the seizure threshold. It should not be administered to children with psychiatric problems or abnormalities of cardiac rhythm. Children who require anticonvulsant therapy and children aged <5 years who have a history of febrile seizures should also avoid mefloquine.

The mixed combination of atovaquone and proguanil, recently released into the US market, adds an additional agent to the chemoprophylactic armamentarium. Atovaquone inhibits the parasite’s mitochondrial electron transport, and proguanil acts on folate to hinder DNA synthesis by the parasite. This combination product does have some effect during the liver stage of malaria (“causal prophylaxis”), so it can be discontinued just a week after the traveling child leaves the area of endemicity. It is effective and safe in children residing in areas of endemicity [25] and in nonimmune adult travelers [22], but detailed studies in pediatric travelers have not been done. Pending further study, it is not yet recommended for children who weigh <10 kg.

Doxycycline is contraindicated in children aged <8 years because of possible staining of developing teeth and because of theoretical concerns about interference with bone growth. It should be taken with plenty of liquid because inadequate swallowing of capsules can lead to esophageal irritation. Photosensitivity occurs in some children who are receiving doxycycline, so use of sunscreen that blocks both ultraviolet A and B radiation is advised for children who are receiving this agent.

Primaquine, an 8-aminoquinoline, has been used for decades to treat persistent hepatic infection with Plasmodium vivax and Plasmodium ovale. Recently, it has been proposed as causal prophylaxis for all forms of malaria. If it were to be used, one would need to rule out glucose-6-phosphate dehydrogenase (G6PD) deficiency in the child, because the use of primaquine in children with this deficiency can cause hemolytic crises. Pri-
In areas where malaria is endemic, efforts at mass chemoprophylaxis have not proved successful. This was primarily due to programmatic problems that limited compliance with the distribution and regular administration of weekly medication. Because of ineffective prophylaxis and incomplete mosquito control measures, the emphasis in developing countries was placed on prompt evaluation and treatment of febrile children who possibly had malaria. Significant decreases in malaria-related morbidity and mortality have not been achieved.

Nonetheless, the idea of administering early presumptive treatment to avert serious complications of malaria is appealing. In travelers who are careful to avoid mosquitoes when visiting areas where the risk of acquiring malaria is relatively low, the risk of side effects from chemoprophylactic medications might be about the same as or even greater than the risk of suffering adversely from malaria. In such cases, one might suggest that chemoprophylaxis be withheld and that presumptive curative therapy be readily available. The German Society of Tropical Medicine and the Swiss Working Group on Travel Medicine are now recommending this approach for travelers to low-risk areas (i.e., parts of Thailand, Mexico, Peru, the Middle East, and some other areas), and this is consistent with the World Health Organization recommendations for travelers to low-risk areas. In the United States, the Centers for Disease Control and Prevention still recommends standard chemoprophylaxis.

However, dependence on presumptive treatment as a means of preventing malaria-induced morbidity and mortality requires that diagnostic methods be accurate and that therapeutic interventions be available and rapidly effective. Clinical findings (e.g., fever, pallor, and splenomegaly) alone have not been completely sensitive or specific in the detection of malaria, but presumptive treatment by parents has sometimes been shown to reduce mortality among children in areas of endemicity [30]. Blood tests that use rapid antigen-detection techniques have been similarly incompletely reliable in field situations [31]. Even in the United States, appropriate diagnostic evaluation of children with malaria is often delayed [32]. Therapeutic interventions are possible, but there can be some morbidity already by the time malaria is suspected and treated. Options for presumptive treatment include chloroquine (for travelers to some limited geographic areas), mefloquine, the combination of atovaquone and proguanil, and quinine, but the side effects associated with therapeutic dosages and compliance challenges can limit the proportion of patients who complete therapy.
Newer rapid-acting antimalarial regimens that involved products such as the combination of artemether and lumefantrine [33] might make even presumptive self-treatment more reliably effective.

In addition, as much as possible, ready access to competent medical care for ongoing monitoring and management must be assured. For travelers to Africa, presumptive therapy cannot replace chemoprophylaxis as the mainstay of malaria prevention among children, especially because of the high risk of P. falciparum malaria and because these diagnostic, therapeutic, and management issues have not been resolved. Whether or not a pediatric traveler received chemoprophylaxis while in an area where malaria is endemic, any febrile illness in such a child should stimulate a prompt and thorough evaluation by a competent medical-care professional.

In conclusion, efforts aimed at the prevention of malaria in children must be multifaceted. Insect avoidance is essential and can prevent the acquisition of a malaria infection. Chemoprophylaxis is effective and usually well tolerated; this serves as a means of preventing symptomatic malaria illness. Rapid treatment of symptomatic malaria is useful in limiting malaria’s morbidity and mortality among travelers who have breakthrough malaria despite preventive efforts. At the same time, children residing in areas where malaria is endemic continue to suffer and die at alarming rates. Global efforts to combat malaria are critical, and continued efforts to perfect an effective vaccine are essential.

References