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TREATMENT AND PREVENTION OF MALARIA IN AFRICAN PREGNANCY

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Abstract

1. Malaria in pregnancy is a major cause of maternal morbidity and mortality worldwide and leads to poor birth outcomes. 2. Treatment consists of antimalarial therapy and supportive care. Treatment choice for malaria infection depends on clinical severity, epidemiologic resistance patterns, and available data about drug safety in pregnancy. In chloroquine-sensitive areas give for first-line therapy (Grade 2C). 3. For treatment of uncomplicated chloroquine-resistant malaria during the first trimester, give quinine combined with clindamycin (Grade 2C). In 2nd or 3rd trimesters, artemi sinin combination therapy or quinine plus clindamycin may be used. For severe chloroquine-resistant malaria, give intravenous artesunate suggested (Grade 2C). 4. Prevention involves chemoprophylaxis and mosquito avoidance. Pregnant travelers must be advised to defer travel to areas where risk of malaria is high until after delivery, if feasible. For pregnant women who cannot defer travel or reside in malarious regions, recommend chemoprophylaxis and mosquito avoidance (Grade1A). 5. For pregnant women who reside in areas of medium and high malaria transmission, we recommend three doses of IPTp with sulfadoxine pyrimethamine rather than two doses (Grade 1A). 6. Sulfadoxine pyrimethamine is given at each scheduled antenatal care visit in the second and third trimesters (at 24 to 26 weeks, at 32 weeks, and at 36 to 38 weeks). Pregnant women with HIV who are not using cotrimoxazole prophylaxis should receive monthly doses. Optimal antimalarial agent, dose, and frequency for IPTp depend on regional transmission intensity, drug resistance patterns, and HIV prevalence. 7. Mosquito avoidance reduces likelihood infection. It is advisable to diminish exposure between dusk and dawn by remaining in screened areas whenever possible, cover exposed skin with clothing, and apply insect repellent.

Key words: Africa, Malaria, Pregnancy, Treatment, Prevention

Introduction

Malaria is a devastating disease that sickens or kills enough people in some African countries to negatively impact not just the country's public health status but also economic and social development (Gallup and Sachs, 2001). It is an important cause of fever and serious illness in returned travelers (Wilson *et al*, 2007). Relative risk of malaria was among returned travelers back from Sub-Saharan Africa than those from Asia or the Americas (Mali *et al*, 2008). Malaria in pregnancy proved to be a major cause of maternal morbidity and leads to poor birth outcomes. Pregnant women are more prone to complications of malaria than non-gravid women (Hill *et al*, 2006).

Review and Discussion

Treatment: Malaria in pregnancy is dangerous for both the mother and the fetus. Thus, pregnant women with malaria must be treated promptly with an effective antimalarial agent to clear parasites rapidly.

However, the safety and efficacy data to the guide management were limited (Orton and Omari, 2008).

Generally, the newer the drug, the more likely it is to be effective (in part because there has been insufficient time for the resistance to emerge), but fewer data would be available on safety in pregnancy. Clinicians therefore have to make treatment decisions based on the clinical severity of infection, epidemiologic resistance patterns, and available data regarding safety of the drug or class of drug in pregnancy. Dellicour *et al*. **(**2010**)** reported that 125 million women in the malaria-endemic areas become pregnant each year and require protection from infection to avoid disease and death for themselves and their offspring. Chloroquine prophylaxis was once a safe approach to prevention but has been abandoned because of drug-resistant parasites, and intermittent

presumptive treatment with sulfadoxine-pyrimethamine is still used to protect the pregnant women throughout Africa, is rapidly losing its benefits for the same reason. Fried and Duffy (2017) stated that women naturally acquire resistance to *Plasmodium falciparum* over successive the pregnancies as they acquire antibodies against parasitized red cells that bind chondroitin sulfate A in the placenta, suggesting that a vaccine is feasible. Pregnant women are an important reservoir of parasites in the community, and women of reproductive age must be included in any elimination effort, but several features of malaria during pregnancy will require special consideration during the implementation of elimination programs.

P. falciparum: Pregnant women with severe *P. falciparum* malaria should receive parenteral therapy; the intravenous route is preferred over the intramuscular route (Tab. 1). Options for therapy include artesunate® or quinine® (plus clindamycin®). In non-pregn- ant adults and children with severe malaria, a mortality benefit was demonstrated with art-esunate® over quinine (Dondorp *et al*, 2010). No trials compared the efficacy of these agents in pregnant women. Historically, quinine plus clindamycin has been recommended during pregnancy given adequate safety data and low cost. Nonetheless, quinine is associated with hypoglycemia even in uncomplicated infections, which may increase risks for both mother and fetus (Taylor and White, 2004).

Many countries are using artemisinin combination therapies (ACTs) as first-line treatment of malaria outside of pregnancy. Data from the use of artemisinins in over 1500 pregnancies during the second and third trimester appeared reassuring, and ACTs were included among the treatment options for uncomplicated malaria in pregnancy in the World Health Organization treatment guidelines (WHO, 2010).

Non-falciparum malaria: Non-*falciparum* malaria refers to infection due to species other than *P. falciparum*: *P. vivax, P. ovale, P. malariae,* and *P. knowlesi* seldom kills, but can be a cause of significant morbidity in pregnancy (Singh *et al*, 2004**)**.

Following treatment of infection due to *P. vivax* or *P. ovale*, non-pregnant patients are treated with primaquine to prevent *P. vivax* and *P. ovale* relapse by eradicating hypnozoite forms that may remain dormant in the liver. Primaquine is contraindicated in pregnancy since it can cause hemolytic anemia in individuals with G6PD deficiency and the fetal G6PD status is uncertain. Therefore, pregnant women should receive a treatment course of chloroquine and then continue once weekly chloroquine until after delivery, when primaquine can be administered.

Plasmodium vivax has the greatest geographic range and burden of disease. Worldwide, estimates of *P. vivax* infections range between 130 and 390 million, with 2.6 billion individuals living at risk of infection (Guerra *et al*, 2006). Endemic *vivax* malaria occurs throughout most of the tropics, including Africa, Asia, the South Pacific, and Central and South America. It may occur at any latitude capable of supporting *Anopheles* mosquitoes (even for brief periods) including temperate latitudes on Korean peninsula, China, Russia, and countries in southwestern Asia such as Iran, Afghanistan, and Tajikistan (Pates and Curtis, 2005).

Lack of *Anopheles* mosquitoes in tropical Micronesia and Polynesia spares these regions, and the absence of Duffy factor on the surface of red blood cells among most Africans spares virtually all of west and central Africa of malaria due to *P. vivax*.

Plasmodium ovale has been described in tropical western Africa and with rare frequency in Southeast Asia and Oceania. The only endemic areas for *P. ovale* outside of Africa were the Philippine archipelago and the island of New Guinea. Of 15,806 blood film examinations at several sites in Indonesia between 1973 & 1989, only 34 infections due to *P. ovale* were identified; the frequency of *P. ovale* relative to *P. falciparum* and *P. vivax* was <1:1000 (Baird *et al*, 1990).

Plasmodium malariae tends to occur with relatively low prevalence in isolated pockets throughout the tropics (Mueller *et al*, 2007).

Plasmodium knowlesi is an emerging human pathogen initially recognized in 2004, with first human case of naturally acquired infection was in 1965 (Chin *et al*, 1965). Malaria due to *P. knowlesi* was described in Malaysian Borneo; as well as in Thailand, Myanmar, Singapore, and the Philippines (Putaporntip *et al*, 2009). However, *P. knowlesi* infection in macaques occurs in India, across Indochina, the Philippine archipelago, and the Indonesian archipelago to the island of Lombok (just east of Bali). Humans live or traveling in all of these regions within range of distribution of the *A. leucosphyrus* vector, especially those living in proximity to macaques, may be considered at risk of infection (CDC, 2009a).

Malaria protection by abnormalities in red cell surface antigens and cytoskeletal proteins: Most red cell genetic defects in human populations (e.g., thalassemia, G6PD defici- ncy, sickle cell anemia) were due to malaria exposure, a disease arisen about 3000 years ago with emergence of agriculture (Wiesenfeld, 1967). Man exhibits variable susceptibility to malarial infection; most of the resist- ance to infection is either genetic, environm- enntal, based upon previous exposure, or access to therapy (Camus and Hadley, 1985). In Sri Lanka, longitudinal studies showed that 20% of the variation in the intensity of malaria was explained by repeatable differences between patients and about half was attributable to host genetics (Mackinnon *et al*, 2000). Mackinnon *et al*. (2005) in Africa found 25% of the total variation in the incidence of hospital admission for malaria was explained by additively-acting host genes, with 2% was due to presence of sickle cell trait. Moxon *et al*. (2011) stated that residence of human erythrocyte is essential for the lifecycle of all zoonotic *Plasmodium* species, the phase of its life cycle to cause malaria. Although the RBCs are highly specialized cells for carrying oxygen to and carbon dioxide away from tissues, it is devoid of or-ganelles and lacks any cellular machinery to synthesize new protein. They added that in order to be able to survive and multiply within the RBC membrane the parasite needs to make many modifications to infected RBC (iRBC). *P. falciparum* modifies RBCs by the insertion of parasite-derived proteins into & onto the membrane that leads to the development of a sophisticated system of antigenic variation (Dzikowski and Deitsch, 2009). Several candidate vaccines used these short periods of vulnerability to produce therapies based on surface antigens of the sporozoite and merozoite forms, with varying success (Riglar *et al*, 2011).

Malarial anemia is capable of causing severe morbidity and mortality especially in children and pregnant women infected with *P. falciparum*. It invades red cells of all ages, multiplies ten-fold within each 24hr cycle and expresses clonally variant antigens on the surface of infected red cells; receptors for ligands on surface of endothelial cells, red cells, and platelets (Snow *et al*, 2005). These variant antigens enable late blood-stage infected red cells to sequester in post-capillary venules. Parasitemia is often high, occasionally exceeding 50%, and the potential for severe anemia, systemic disease, and death is considerable. *P. vivax* and *P. ovale* have a strong preference to young red cells with limited parasitemia levels to about 1 to 2%. *P. malariae* invades red cells of all ages, with relatively limit parasitemia (<1 to 2%) and mild symptoms (Greenwood, 1997).

Severe malarial anemia (SMA) is common in areas of very high malarial transmission; commonly in young children and pregnant women, defined as a hematocrit <33%, in malarial endemic areas of Africa varies between 31 & 91% in children, and between 60 & 80% in pregnant women (Schellenberg *et al*, 2003). In children living a malarial endemic area in southern Cameroon the anemia prevalence (hemoglobin < 11 g/dL) was

highest in the six-month-old age group (47%), 42% in children <3 years of age and 21% in those 3 to 5 years of age. Placental malarial infection was the primary risk factor for anemia in the six-month old children (Cornet *et al*, 1998).

Anemia features of *P. falciparum* in endemic areas infection are broad. Infections present in semi-immune and immune children and adults as an uncomplicated febrile illness, fever after release of merozoites from ruptured, infected red cells. Anemia, thrombocytopenia, massive splenomegaly, hepatomegaly, jaundice, and splenic rupture can occasionally occur (Bedu-Addo and Bates, 2002). Not only may acute infection present with anemia and/or cerebral malaria, respiratory distress and hypoglycemia, but chronic, repeated malarial infection may also lead to severe anemia.

Non-immune patients may exhibit a number of clinical syndromes including anemia, coma, respiratory distress, and hypoglycemia, with a high frequency of concurrent bacteremia (Berkley *et al*, 1999). Children may present with mild, moderate or even severe anemia with or without other syndromes of severe disease (English, 2000).

Chronic anemia in chronic malaria: Many children may present with severe anemia, with negative blood smear for malaria, but respond to antimalarial treatment (Roberts *et al*, 2005)...

Hematologic features: anemia of *P. falciparum* is typically normocytic and normochromic, with a notable absence of reticulocytes (Roberts *et al*, 2005). Microcytosis and hypochromia may be present due to the very high frequency of thalassemia trait and/or iron deficiency in many, but not all, of the endemic areas (Newton *et al*, 1997).

Black water fever (BWF): A less common form of anemia in malaria is characterized by intravascular hemolysis, the sudden appearance of hemoglobin in the urine, and renal failure, classically associated with irregular use of quinine (Stephens, 1937). BWF is sometimes difficult to relate to malaria, because parasitemia can be missed due to synchronous lysis of all infected red cells. In Africa, BWF cases showed sudden hemolysis associated with malaria, glucose-6-Phos-phate dehydrogenase deficiency, and use of quinine (Naqvi *et al*, 1996). BWF virtually disappeared when chloroquine superseded quinine. But, in European expatriates living in Africa, BWF has been associated with use of the antimalarial agent's halofantrine, quinine, and mefloquine (Bruneel *et al*, 2001).

Anemia in *P. vivax* malaria: *P vivax* can cause severe disease, including anemia and severe hemolysis, clearly associated with anemia during pregnancy, along with low birth weight of the children of these infected mothers (Rodriguez-Morales *et al*, 2006).

Relapse: Relapse may occur in the setting of infection due to *P. vivax* and *P. ovale* infection, since the life cycle of these two species includes hypnozoites, a quiescent stage in the liver. Liver stage does not cause clinical symptoms, but relapsing disease occurs in the setting of reactivation of hypnozoites with release into the systemic circulation. Late-onset or relapsing disease can occur up to many months after initial infection, even after appropriate treatment (or prophylaxis) of the primary blood stage infection. The timing, risk, and extent of relapse vary with geography of transmission (Schwartz *et al*, 2003). Generally, the relapse risk for strains acquired in tropical Asia is about 80 to 100%; most relapses occur within 30 days of infection and up to two to four relapses may occur. In contrast, the relapse risk for strains acquired in temperate zones is about 30%; most relapses occur 6 to 12 months following infection, and more than one relapse is rare. In India, however, *P. vivax* behaves more like temperate than tropical strains in all of these regards (Joshi *et al*, 2008). Relapse due to *P. ovale* is uncommon with limited data. Most reports describe relapse within 17-255 days (Chin and Coatney, 1971). But, there was a report of relapse four years following infection (Trager and Most,

1963).

Prevention: Major tools for prevention of malaria in pregnant women include chemoprophylaxis and mosquito avoidance.

Chemoprophylaxis: The pregnant travelers must be advised to defer travel to areas where risk of malaria is high until after delivery, if feasible. For the pregnant, non-immune women who cannot defer travel, chemoprophylaxis is recommended. The agents of choice are chloroquine for travel to areas with chloroquine-sensitive malaria and mefloquine for travel to areas with chloroquine resistant malaria (CDC, 2012).

Pregnant women living in endemic areas who have developed natural immunity (due to prolonged exposure to malaria) benefit from chemoprophylaxis against malaria (Garner and Gülmezoglu, 2003). Implementation of continuous prophylaxis is not practical on a widespread scale. An effective alternative approach to reduce malaria infection risk for women with prior immunity in endemic areas is Intermittent Preventive Treatment duri-ng pregnancy (IPTp) (Menéndez *et al*, 2010). The optimal antimalarial agent, dose, and frequency for IPTp depend on regional trans-mission intensity, drug resistance patterns, and HIV prevalence (Taylor *et al*, 2012).

For pregnant women in areas with medium and high malaria transmission, WHO (2012) recommended to provide IPTp with sulfadoxine pyrimethamine (SP) at each scheduled antenatal care visit in the second and third trimesters, as well as recommended four focused antenatal care visits as standard care: a first visit in the first trimester, a second visit at 24 to 26 weeks of gestation, a third visit at 32 weeks, and a fourth visit at 36 to 38 weeks). Each dose suppresses or clears any existing asymptomatic infections from the placenta and provides up to six weeks of post-treatment prophylaxis. The previous recommendation for only two doses of SP one month apart resulted in a large number of missed opportunities for delivering IPTp during antenatal care and providing it close to the time of delivery, resulting in poorer pregnancy outcomes. In a systematic review and meta-analysis of trials of IPTp with SP during pregnancy that compared ≥3 dose regimens with the standard 2 dose regimen, the ≥3 dose regimens resulted in fewer low birth weight infants with RR 0.80, 95% CI 0.69-0.94; 134/1000 vs. 167/1000, less placental malaria with RR 0.51, 95% CI 0.38-0.68; 32/1000 versus 63/1000, and less moderate to severe maternal anemia with RR 0.60, 95% CI 0.36-0.99; 22/1000 vs. 36/1000 (Kayentao *et al*, 2013).

The benefit of IPTp diminishes as local drug resistance increases. In a study among 880 pregnant women in Muheza, Tanzania, where SP resistance has reached 68%, IPTp with SP did not decrease the odds of placental malaria or increase mean maternal hemoglobin or neonatal birth weight (Harrington *et al*, 2011). This underscores the need for more research to identify effective alternative regimens for IPTp.

HIV infection: Pregnant women with HIV infection require more intensive IPTp dosing to reduce the risk of placental malaria if they are not using cotrimoxazole prophylaxis for opportunistic infections (Filler *et al*, 2006). Among HIV-positive women in their first or second pregnancy, monthly IPTp with SP resulted in less placental malaria and higher neonatal birth weights than two doses IPTp over the range of resistance tested up to 39% (ter Kuile *et al*, 2007).

Mosquito avoidance: Avoidance of mosquitoes is important for reducing the likelihood of malaria infection. Mosquitoes capable of transmitting malaria infection (*Anopheles* species) usually feed at night; thus, it is advisable to diminish exposure between dusk and dawn by remaining in screened areas whenever possible, using mosquito netting (ideally treated with permethrin), covering exposed skin with clothing, and applying insect repellent. The approach to protection against arthropod bites is influenced by the level of protection that is needed in a specific situation. For example, a

combination of chemically-treated gear and clothing and a strong chemical repellent may be necessary in areas with high concentrations of disease-carrying arthropods (CDC, 2009). Anyhow, travelers to malarious areas should receive instructions regarding methods to prevent bites from Anopheles mosquitoes; such measures also help reduce bites from sandflies, ticks and other mosquito species. These include: Avoiding outdoor exposure between dusk and dawn (when *Anopheles* mosquitoes feed) Wearing clothing that reduces the amount of exposed skin Wearing insect repellant Sleeping within bed nets treated with insecticide (e.g., permethrin). Staying in well-screened or air-conditioned rooms (Fradin and Day, 2002). In contrast, milder repellents may be sufficient for preventing nuisance bites in areas with low levels of disease vectors. Insect repellents recommended by the CDC (2008) for reducing the risk of malaria include DEET and picaridin. DEET (30 to 50%) is generally protective for at least 4 hours, although lower percentage preparations provide a shorter duration of protection. When used appropriately, DEET is safe for infants and children over the age of 2 months. Picaridin is a synthetic repellant. This agent (20% concentration) and DEET (35% concentration) have comparable efficacy for the protection against malaria vectors up to eight hours after application (Kimani *et al*, 2006). The highest concentration of picaridin sold in the US is 15%, but not sufficient data to support adequate protection against *Anopheles* at this concentration.

Insect repellents: Among repellents, some act as agonists at olfactory receptors, binding the receptors and blocking recognition of suitable prey. Others antagonize olfactory receptors and actively reverse a normally attractive scent into a deterring scent. Due to highly divergent receptors, the same compound may act as an agonist in one species and an antagonist in another (Bohbot *et al*, 2011). Guidelines regarding the safe and effective use of insect repellents in order to maximize effectiveness and minimize side effects were issued by the United States (US) Environmental Protection Agency (EPA, 1996). These are particularly important when using DEET-based repellents: 1- Use just enough repellent to lightly cover but not saturate the skin. 2- Repellents should be applied to exposed skin, clothing, or both, but not under clothing. 3- A thin layer can be applied to the face by dispensing repellent into the palms, rubbing hands together, and then applying to the face. 4- Repellent should be washed from the palms after application to prevent contact with the eyes, mouth, and genitals. 5- Do not use repellents over cuts, wounds, inflamed, irritated, or eczematous skin. 6- Do not inhale aerosols, spray them in enclosed spaces or near food, or get them into the eyes. 7- Do not apply insect repellent to the hands of small children, as it will inevitably be rubbed into the eyes. 8- Frequent reapplication of repellent is unnecessary. 9- The areas treated with repellent should be washed with soap and water once the repellent is no longer needed. But, protection is shortened by swimming, washing, sweating, wiping, exercise, and rainfall (Schofield *et al*, 2007).

The most effective insect repellents are: 1- DEET (N, N-diethyl-3-methylbenzamide), 2-Picaridin (KBR 3023), 3- PMD (P-methane-3, 8-diol), 4- Bio-UD, and 5- IR 3535. These agents are not equal in their efficacy and provide varying degrees of protection against different arthropods.

1- DEET (N, N-diethyl-3-methylbenzamide) is effective against mosquitoes, biting flies, chiggers, fleas, and ticks. DEET has been in use for more than 50 years and was considered the "Gold standard" of insect repellents (Pickett *et al*, 2008). No other compound covers as broad a spectrum of arthropods or offers the extended duration of action of DEET (Katz *et al*, 2008). There are micro-encapsulated formulations (e.g., 3M™ Ultrathon™), which increase the period of evaporation (and hence repellency) while reducing absorption by the skin. These

products have made it possible to decrease the concentration of DEET without sacrificing its duration of action (Casting *et al*, 2008).

DEET is available in many products with concentrations ranging from less than 10% to more than 75%. The effectiveness of DEET plateaus at approximately 30 percent, but higher concentrations provide longer duration of protection (Fradin and Day, 2002) Products with concentrations around 10% are effective for periods of approximately two hours; a concentration of about 24% provides an average of five hours of protection. Protection is shortened by swimming, washing, rainfall, sweating, and wiping AAP (2011) mentioned that "I would talk to your child's doctor or consult a travel clinic. You are basically trading off the risk of a poison with the risk of difficult to treat illnesses. I'm not an expert but based on my research I use DEET when I see mosquitoes"

A prudent approach is to select the lowest concentration effective for the amount of time spent outdoors. Products with 10 to 35% DEET are adequate in most circumstances. Higher concentrations should be reserved for situations in which insect infestation is high, elevated temperatures and humidity may limit evaporation, or time outdoors would exceed three to four hours. Although serious adverse reactions to the DEET are uncommon, excessive absorption through the skin can cause dermatitis, allergic reactions, and rare neurotoxicity (CDC, 1989). DEET can damage some plastics, as well as clothes made from synthetic fibers such as spandex or rayon, and some patients dislike the oily and sticky skin sensation that DEET can cause. Repellents containing DEET may reduce efficacy of sunscreens applied simultaneously, although the labeling of combined products containing both components should have taken this into account and the sunscreen component should provide the stated sun protection factor.

a- Use in children: as directed, DEET appeared to be safe for children older than two months of age (Koran *et al*, 2003). However, adverse neurologic effects, such as encephalopathy, have been reported with massive exposure and chronic use (Fradin, 1998). Overall, fewer than 20 cases were reported worldwide and each developed in the setting of inappropriate use (oral ingestion or repeated exposure to high concentrations), with at least three fatalities (Briassoulis *et al*, 2001). Hypersensitivity pneumonitis in the child following the inhalation of a DEET-containing insect repellent was reported (Morton *et al*, 2006). Undoubtedly, all physicians accepted the American Academy of Pediatrics (AAP, 2011) recommended that children younger than two months of age should not use products with DEET. For older infants and children, repellents with 10 to 30% DEET should be safe and effective when used according to the directions on the product labels. Products containing both DEET and sunscreen are not recommended for children because reapplication (as may be necessary for the sunscreen component) would result in an excessive exposure to DEET. DEET-containing sunscreens should not be reapplied and should be washed off when back indoors or protection is no longer needed (Garrettson, 1997).

b- Use in pregnancy: The recommendations for DEET use in pregnant and lactating women do not differ from those for non-pregnant adults (Roggelin and Cramer, 2014). CDC (2007) advised pregnant women to take precautions to reduce their risk of acquiring arboviral infections (e.g., West Nile virus) by avoiding mosquito bites through use of protective clothing and DEET-based repellents.

First trimester exposure of rats and rabbits to DEET did not result in an increased risk of malformations in offspring, although one study using a dose several-fold higher than the normal human dose reported an increase in low birth weight (Schoenig *et al*, 1994). There are no human data for first trimester exposure. A double-blind, randomized, ther-

apeutic trial of insect repellents for the prevention of malaria in 897 pregnant women did not report any adverse neurologic, gastrointestinal, or dermatologic effects in wom-en who applied a median total DEET dose of 214g per pregnancy; range = 0 to 345g (Mc-Gready *et al*, 2001). No adverse effects were noted on fetal/infant survival, growth, or development up to one year of age. DEET was detected in four cord blood samples from a randomly selected subgroup of 50 DEET users.

2- Picaridin: Picaridin (KBR 3023), a plant-derived piperidine compound, is effective against mosquitoes, ticks, and the sand fly *Phlebotomus papatasi* (Badolo *et al*, 2004) This agent has been successfully used for years in Europe and Australia. In the US, it is available in a 20% solution (Sawyer™ Insect Repellent), as well as in a 7 or 15% solution (as Cutter Advanced™ and Cutter Advanced Sport™, respectively).

Higher concentrations of picaridin (e.g., 20%) have similar efficacy to DEET when used for short periods. But, DEET has a longer duration of action (Frances *et al*, 2004). Field trials comparing the efficacy of picaridin to DEET for protection against mosquitoes (*Anopheles gambiae*) were performed with varying concentrations of picaridin; these trials demonstrated comparable potency between high strength picaridin and DEET up to about five hours after application (Costantini *et al*, 2004).

Adverse effects: No toxicity in humans has been reported where it has been in long-term use, although hepatic toxicity has been reported in rats at very high doses (Astroff *et al*, 2000).

Picaridin has an excellent tolerability profile, in contrast to DEET. Picaridin is odorless, non-sticky, and non-greasy; it also does not irritate skin, stain fabrics, or degrade plastics.

3- P-menthane-3,8-diol (PMD): PMD is the active ingredient in oil of lemon eucalyptus and in the most widely-used Chinese insect repellent, quwenling. It is a plant-derived ingredient that has been listed by the Environmental Protection Agency (EPA) as effective against mosquitoes, biting flies, and gnats (Klun *et al*, 2006). In the United States, PMD is available as 65% PMD (Repel Lemon Eucalyptus Insect Repellent Lotion and Spray Lotion™ and Survivor Lemon Eucalyptus Insect Repellent™) and 10% PMD (Off! Botanical Insect Repellent™).

Studies of efficacy are limited (Carroll and Loye, 2006). Generally, PMD is approximately one-half as effective as DEET, such that a 30% PMD product would protect as well as a 15% DEET product (Frost, AC, 2005). As an example, one comparative trial of 40% PMD and 25% DEET reported a mean protection time of 3.8 hours with PMD compared with 5.6 hours with DEET (Barnard *et al*, 2002).

Adverse effects: Toxicity in animals was limited to eye irritation, with one human report of skin irritation, but neither problem is common. CDC recommends avoiding eye contact and not using PMD on the faces and hands of small children (EPA, 2007)

a- Use in children: The compound has not been adequately tested in children younger than three years old and should not be used in this group (CDC, 2009).

3- BioUD: BioUD is a tomato-derived arthropod repellent registered by the US/EPA (2007), and assigned the lowest toxicity rating. Its active ingredient is 7.75% 2- UNdecan-one. BioUD is available in the US as Bite-Blocker™.

BioUD repels mosquitoes similarly to products containing up to 30% DEET in one report (Witting-Bissinger *et al*, 2008). A study cited on the manufacturer's website indicated that BioUD was comparable to 7% DEET (Bohbot and Dickens, 2010). Very high concentrations of BioUD and DEET appeared to have similar repellency against ixodid ticks, but this cannot necessarily be extrapolated to the lower concentrations intended for human use (Bissinger *et al*, 2009).

4- IR 3535: IR 3535 is a synthetic repellent

available in the United States as Avon Skin-So-Soft Bug Guard plus IR 3535 Expedition™. There are limited studies comparing IR 3535 to DEET or picaridin, but appeared to be the least effective of the three in one study, although it compared favorably with DEET in another (Cilek *et al*, 2004). One study showed a long duration of action (Carroll, 2008).

Less effective and ineffective agents: Other agents marketed as insect repellents include citronella, and various botanical oils, vitamin supplements, and herbal preparations. There are also a variety of electronic devices and repellent-impregnated wristbands available.

1. Citronella ((lemongrass oil), is a plant-based repellent that lacks the broad spectrum of activity and duration of action of DEET, but with less harmful effects compared to its available market counterpart DEET (Agrawal *et al*, 2017). Frequent application may compensate for its limited duration of effectiveness, although animals showed that citronella-based repellents to be potential dermal sensitizers (Fradin and Day, 2002).

2. Botanical oils: Various botanical oils, including sandalwood, geranium, soybean, and others, have been used alone or in combination for repelling mosquitoes. The majority of studies of botanical oils and botanical-based repellents showed that the protection offered by these agents was far inferior to DEET, PMD, or picaridin (Girgenti and Suss, 2002).

3. Ingestion of strong-smelling foods or other substances: Claims that ingestion of odiferous substances, such as garlic, onions, cruciferous vegetables or mineral sulfur, can repel biting insects have not been substantiated. Barnard and Xue (2004) estimated mean protection time (eMPT) responses for four synthetic mosquito repellents (Autan [10% KBR3023], IR3535 [7.5%], Off! [15% DEET], Skinsations [7% DEET]) and eight natural (primarily plant extracts and/or essential oils) product-based repellents (Bite Blocker [2% soybean oil], Bygone, Gone! Natrapel [10% citronella], Neem Aura, Sunswat, MosquitoSafe [25% geraniol], and Repel [26% p-menthane-3,8-diol]) were tested in the laboratory against mosquitoes. They divided the average eMPT for each repellent by eMPT for 7% DEET (Skinsations), the order of repellent effectiveness and the corresponding repellency index (R,) was Repel (1.7) > Bite Blocker (1.5) = Autan (1.5) = Off! (1.5) > Skinsations (1.0) > IR3535 (0.8) > MosquitoSafe (0.6) > Natrapel (0.5) > Neem Aura (0.3) = Sun Swat (0.3) = Bygone (0.3) > Gone (0.2).

4- Vitamin supplements and herbal remedies: No controlled scientific study of ingested vitamin or herbal remedies showed these interventions to protect users from biting insects (Day, 2009).

5- Electronic devices: Electronic mosquito repellents are devices that emit high-pitched sounds that are generally inaudible to the human ear. A Cochrane review of 10 field studies concluded there was no evidence that the devices repelled mosquitoes to any degree (Emanate *et al*, 2007).

6- Wristbands: Wristbands impregnated with insect repellents are not effective, regardless of the repellent used. Karunamoorthi and Sabesan (2009) in India conducted in urban locality of human test subjects were exposed to natural populations of mosquitoes for a 12hr (18.00-06.00) night time period. The fabric strips (anklets, wristbands, shoulder, and pocket strips) were impregnated with DEET at two different concentrations of 1.5mg/cm^2 and 2.0 mg/cm^2. They concluded that repellent activity of DEET-impregnated anklets, wristbands, shoulder, and pocket strips were dose-dependent. Certainly, DEET -impregnated fabric strips can be used as an effective potential personal protection measure in order to avoid those insects/ mosquitoes that prefer to feed outdoors or those that feed in the early evening.

Use of insecticide treated bed nets (ITNs) is an important tool for reducing the likelihood of malaria among pregnant women in endemic areas (ter Kuile *et al*, 2003). A

Cochrane review of the impact of ITNs during pregnancy included five randomized trials (four trials from sub-Saharan Africa compared use of ITNs to no nets and one trial from Thailand compared use of ITNs with use of untreated nets). In the African trials, use of ITNs significantly reduced the risk of placental malaria in all pregnancies (RR 0.79, 95% CI 0.63-0.98). In first through fourth pregnancies, use of ITNs significantly reduced the risk of the low birth weight (RR of 0.77, 95% CI 0.61-0.98) and stillbirth/abo-rtion (RR 0.67, 95% CI 0.47-0.97). Trial from Thailand showed significant reductions in anemia and stillbirth in all pregnancies, but no significant change in rates of LBW or clinical malaria (Gamble *et al,* 2006)

Insecticide treated nets: Bed nets are a sensible physical barrier precaution against malaria-transmitting mosquitoes since the major malaria vectors bite during the night as; *An. gambiae* and *An. funestus* (Hamon, 1963). Addition of a chemical barrier in the form of pyrethroid treatment to bed nets provides protection, even if the net is torn.

Pyrethroids are the major insecticides used routinely for bed net treatment. Newer long-lasting insecticidal nets (LLINs) are washing proof pyrethroid impregnated nets; they may be used for about five years, after which they must be replaced because of wear (with holes) and decreased pyrethroid content. Only LLINs should be deployed in control and elimination programs.

Widespread community use of ITNs reduces the proportion of mosquitoes surviving long enough to transmit malaria; each attempt at a blood meal from an ITN-protected human results in a potentially lethal insecticide exposure for the mosquito (Curtis *et al,* 2006). Alonso *et al.* (1991) in the Gambia showed that the community-wide ITN coverage can reduce malaria-attributable mortality by 30% and overall children mortality by 37%. Use of pyrethroid impregnated nets thus far did not appear to have toxicity for humans but further evaluation was warranted (Wang *et al*, 2007).

For high frequency of adherence to ITN use, health education in communities is essential for assuring correct installation, hours of use, and maintenance of the ITNs. Follow up of ITNs provided to a community in Tanzania several years earlier confirmed that individuals continued to use the nets, in part because of their additional impact on other nuisance insects such as bedbugs (Lengeler, 2005). But, some have postulated that use of ITNs for reducing the burden of malaria may slow development of immunity to infection among children; this does not appear to be the case. After nearly four years of community ITN use in Tanzania, morbidity among very young children diminished, and morbidity among older children compared to aged-matched controls in villages without nets. In a study of 130,000 persons in western Kenya the mortality rate for children <1 year was significantly decreased after 4 years of ITN use with no increase in mortality among older children (Lindblade *et al*, 2004). Serological studies have shown diminished levels of antimalarial antibodies after prolonged ITN use in a community, but the clinical significance was uncertain (Askjaer *et al*, 2001).

There was a concern about the emergence of pyrethroid resistance among major mosquito vectors; laboratory detection of resistance genes may or may not correlate with epidemiologic observations. While genes for pyrethroid resistance have been demonstrated among mosquito vectors in the Ivory Coast, ITNs remain effective for killing mosquitoes and preventing malaria (Henry *et al*, 2005). However, in southern Benin, failure of the pyrethroid-based ITNs to kill mosquitoes has been reported.

Use of pyrethroids for ITNs is more economical than for indoor residual spraying (IRS). Comparing pyrethroid for ITN versus IRS, comparable effects on mosquito populations and malaria morbidity were reported, although IRS required six times as much insecticide as bed net treatment (Curtis *et al,*

1998).

Drug Safety: The pharmacokinetics of most antimalarials in pregnancy remains largely undefined. Chloroquine is well-tolerated and has not been shown to be harmful in pregnant women. Quinine and quinidine can be used in pregnant women with P. falciparum infections at recommended therapeutic doses, and do not lead to more adverse pregnancy outcomes compared with the malaria infection itself. At high doses, quinine is reported to have a weak abortifacient effect, but such levels are not achieved with recommended therapeutic doses. Quinine has also been associated with maternal and fetal hypoglycemia (Phillips, 1989). Unfounded fears of toxicity and unjustified withholding of quinine has led to many fatal maternal outcomes. Quinine is not contraindicated in pregnancy-associated malaria and should be used when needed. Glucose levels should be monitored due quinine capacity to release insulin. (Looareesuwan *et al*, 1985)

Published data on mefloquine® use during pregnancy have demonstrated that pregnant women who took mefloquine for treatment of malaria did not have an increased risk of adverse pregnancy outcomes compared with the background rate in the general population. Based on these studies, the US/FDA categorized mefloquine as category B. Mefloquine is effective for prevention of malaria due to chloroquine-sensitive and chloroquine-resistant *P. falciparum*, as well as the other malaria species that cause human malaria. In a study of almost 140,000 travelers to East Africa, the prophylactic efficacy of mefloquine was 91% (Steffen *et al,* 1993). El-Bahnasawy *et al.* (2010) in Egypt treated twenty malarial patients, who were recruited from Peace Keeping Mission Forces in Africa with Mefloquine. They concluded that the best therapeutic response for locally acquired malaria infection was the monotherapy-based one such as chloroquine or mefloquine. González *et al*. (2018) stated that Mefloquine was more efficacious than sulfadoxine-pyri-methamine in HIV-uninfected women or daily cotrimoxazole prophylaxis in HIV-infect-ed pregnant women for prevention of malaria infection and was associated with lower risk of maternal anemia, no adverse effects on pregnancy outcomes (such as stillbirths and abortions), and no effects on low birth weight and prematurity. But, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.

Amodiaquine is used in Africa, where multidrug resistant *P. falciparum* is common. A randomized trial reported that amodiaquine alone or in combination with sulfadoxine-pyrimethamine (SP) was significantly more effective than chloroquine or SP. (Sulfadoxine and pyrimethamine target enzymes involved in folate synthesis; pyrimethamine targets dihydrofolate reductase (DHFR), and sulfadoxine acts on dihydropteroate synthase (Miller *et al*, 1986). Sulfadoxine-pyrimetha-mine (SP; brand name Fansidar®) is available in a fixed-dose tablet; because the components act on enzymes in the same pathway, it is not considered a combination therapy. Mild adverse effects include gastrointestinal upset and headache. Mild bone marrow suppression may occur, and sulfadoxine can precipitate hemolysis in patients with G6PD deficiency. Severe cutaneous toxicity due to the sulfa moiety can occur, including erythe-ma multiform, Stevens-Johnson syndrome, and toxic epidermal necrosis (Gimnig *et al*, 2006).

However, *P. falciparum* resistance to sulfa-doxine-pyrimethamine is widespread in most malaria-endemic regions. The treatment with amodiaquine was not associated with an increased risk of preterm birth, stillbirth, or congenital anomalies, but the trial was too small to conclude that its use was safe for the fetus. In general, amodiaquine is not used by clinicians in the United States or United Kingdom due to the risk of agranulocytosis (Tagbor *et al*, 2006).

Data on the safety of artemisinin drugs in

pregnancy, especially during the first trimester, are limited. The World Health Organization has advised that artemisinin drugs be avoided in the first trimester unless the treatment is believed to be life saving for the mother and other antimalarial drugs are contraindicated, are likely to be ineffective (e.g., for treatment of malaria acquired in regions with the partial quinine resistance, such as Southeast Asia), or failed (WHO, 2010). Among 773 women with first-trimester pregnancies treated for malaria in Thailand, the risk of miscarriage was similar for women treated with chloroquine, quinine, or artesunate (26, 27, & 31%, respectively). In the same study, the risk of congenital abnormalities in neonates was not statistically increased in treated pregnancies or different among the three drugs (0/262, 2/258, & 2/44) respectively vs. 1% in women with neither malaria nor treatment (McGready *et al*, 2012). In experimental animal studies using artemisinin compounds, fetal resorption early in gestation was reported (McGready *et al*, 2003). Animal studies suggested that depletion of embryonic erythroblasts might underlie artesunate-associated embryo toxicity. But, erythrocytes developed over a longer period of time in primates and thus similar effects may not be observed in humans (Boareto *et al*, 2008).

More data in humans are available for second and third trimester exposure: artemisinin derivatives have not been found to be harmful to the fetus during this period of pregnancy and are acceptable for use during these trimesters (McGready *et al*, 2005).

Tetracycline, doxycycline, primaquine, & halofantrine are contraindicated in pregnancy (Nosten *et al*, 2006). Doxycycline is avoided during pregnancy because other tetracyclines have been associated with transient suppression of bone growth and with staining of developing teeth, but available data do not show teratogenic effects from doxycycline. Pregnancy is a contraindication for primaquine therapy since it is not possible to assess G6PD status of a fetus in utero (Baird and Hoffman, 2004). Primaquine and the tetracyclines should be avoided while breastfeeding (White, 1996). There are no human data on halofantrine exposure in pregnancy. In severe malaria infection, fetal assessment is recommended, as no reassuring fetal heart rate tracings and fetal growth restriction are common. One author's (PC) experience that amniotic fluid volume decreased during febrile periods to normalize with defervescence. Assuming available resources, a reasonable program of surveillance consists of serial ultrasound examinations for assessment of fetal growth and amniotic fluid (Schmiegelow *et al*, 2013).

Generally speaking, *P. falciparum* infections adversely affect the pregnant woman. Anti-malarial treatment failure is common with duration of persistent parasite carriage following anti-malarial treatment in pregnancy (McGready *et al*, 2012).

Laochan *et al*. (2015) reported that interval of *falciparum* malaria to recrudescence in pregnancy could be prolonged, regardless of anti-malarial treatment used. In areas with intercalated *P. vivax* occurred and the treated, time to recrudescence of *P. falciparum* could be prolonged. In this area of low, seasonal malaria transmission, recrudescence occurred after day 42 in approximately 15% and after day 63 in 5 %, of pregnant women. Accurate characterization of drug efficacy in pregnancy required follow-up to delivery or day 63, whichever occurs last.

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Table 1: Uncomplicated malaria in pregnant women*

Region infection acquired	**Recommended drug and adult dose**
Chloroquine-sensitive *Plasmodium* species Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East. Infections acquired in the newly independent States of the former Soviet Union and Korea to date have been uniformly caused by *P. vivax* and should therefore be treated as chloroquine-sensitive infections.	Chloroquine (Aralen and generics) 600 mg base (=1000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours. Total dose: 1500 mg base (=2500 mg salt). *OR* Hydroxychloroquine (Plaquenil and generics) 620mg base (=800 mg salt) po immediately, followed by 310mg base (=400 mg salt) po at 6, 24, & 48 hrs. Total dose: 1550 mg base (=2000 mg salt).
Chloroquine resistant *P. falciparum* * All malarious regions except those specified as chloroquine-sensitive listed in the box above. Middle Eastern countries with chloroquine-resistant *P. falciparum* as Iran, Oman, Saudi Arabia, and Yemen.	Quinine sulfate PLUS Clindamycin Quinine sulfate: 542 mg base (=650mg salt)¥ po tid x 3 or 7 days Clindamycin: 20 mg base/kg/day (up to 1.8 grams) po divided tid x 7 days
(See "Overview of non-falciparum malaria" for regions with chloroquine-resistant *P. vivax*)	Quinine sulfate Quinine sulfate: 650 mg salt po tid x 7 days §

Table 2: Features indicating a poor prognosis in severe malaria (White, NJ, 1996)

Clinical features	1- Impaired consciousness* 2- Repeated convulsions (3 in 24 hr) 3- Respiratory distress (rapid, deep, labored breathing) 4- Substantial bleeding 5-Shock
Biochemical features	1- Renal impairment (serum creatinine, >3 mg/dl [>265 µmol/liter]) 2- Acidosis (plasma bicarbonate, <15 mmol/liter) 3- Jaundice (serum total bilirubin, >2.5 mg/dl [>43 µmol/liter])** 4- Hyperlactatemia (venous lactate, >45 mg/dl [>5 mmol/liter]) 5- Hypoglycemia (blood glucose, <40 mg/dl [<2.2 mmol/liter]) 6-Elevated aminotransferase levels (>3 times normal)
Hematologic features	Parasitemia (>500,000 parasites/mm3 or >10,000 mature trophozoites & schizonts/ mm3)*** ≥5% of neutrophils contain malaria pigment
* Deeper coma, worse prognosis, **Combination of deep jaundice and renal failure is particularly grave. ***Trophozoites are mature parasites in which pigment is visible under light microscopy	

Table 3: Treatment of uncomplicated non-*falciparum* malaria

Variant	Drug	Adult dosing	Pediatric dosing	Pregnancy*
P. vivax *P. ovale* (chloroquine-sensitive)	Chloroquine or Hydroxy-chloroquine plus Primaquine	Chloroquine 600mg base (=1000mg salt) orally immediately, followed by 300mg base (=500 mg salt) orally at 6, 24, & 48 hrs. Total dose: 1500mg base (=2500 mg salt) Hydroxychloroquine 620mg base (=800 mg salt) orally immediately, followed by 310mg base (=400mg salt) orally at 6, 24 & 48 hrs. Total dose: 1550mg base (=2000mg salt) Primaquine 30mg base orally once daily for 14 days	Chloroquine 10mg base/kg orally immedia-tely, followed by 5mg base/kg orally at 6, 24, & 48 hrs. Total dose: 25mg base/kg Hydroxychloroquine 10mg base/kg orally imme-diately, followed by 5mg base/kg orally at 6, 24 & 48 hrs. Total dose: 25mg base/ kg Primaquine 30mg base orally once daily for 14 days	Chloroquine or Hydroxy-chloroquine
Chloroquine-resistant P. vivax§ (Papua New Guinea and Indonesia)	Mefloquine or Atovaquone-proguanil (Malarone) plus Primaquine	Mefloquine 648mg base (=750mg salt) orally as initial dose, followed by 456mg base (=500mg salt) orally given 6-12 hours after initial dose (total dose = 1250mg salt) Atovaquone-proguanil Adult tab = 250mg atovaquone / 100mg proguanil. 4 adult tabs orally once daily for 3 days Primaquine (as above)	Mefloquine 13.7mg base/kg (=15mg salt/ kg) orally as initial dose, followed by 9.1mg base/kg (=10mg salt//kg) orally given 6-12 hrs after initial dose (total dose = 25mg salt/kg) Atovaquone-proguanil Peds tab=62.5 mg ato-vaquone/ 25mg proguanil. All doses given orally once daily for 3 days: 5-8 kg: 2 peds tabs; 9-10 kg: 3 peds tabs; 11-20 kg: 1 adult tab; 21-30 kg: 2 adult tabs; 31-40 kg: 3 adult tabs; >40kg: 4 adult tabs Primaquine (as above)	Mefloquine (only)
	B. Quinine plus one of following: Doxycycline Tetracycline plus Primaquine	Quinine¥ 542mg base (=650mg salt) orally three times daily x 3 to 7 days Doxycycline 100mg orally twice daily x 7 days Tetracycline 250mg orally four times daily x 7 days Primaquine (as above)	Quinine¥ 8.3mg base/kg (=10mg salt/kg) orally three times daily x 3 to 7 days Doxycycline 2.2mg/kg orally twice daily x 7 days Tetracycline 25mg/kg/day orally divided four times daily x 7 days Primaquine (as above)	Quinine (only
P. malariae *P. knowlesii*	Chloroquine Or Hydroxy-chloroquine	Chloroquine (as above) Hydroxychloroquine (as above)	Chloroquine (as above) Hydroxychloroquine (as above)	Chloroquine or Hydroxy-chloroquine
Variant	**Drug**	**Adult dosing**	**Pediatric dosing**	**Pregnancy***
P. vivax *P. ovale* (chloroquine-sensitive)	Chloroquine or Hydroxy-chloroquine plus Primaquine	Chloroquine 600mg base (=1000mg salt) orally immediately, followed by 300mg base (=500 mg salt) orally at 6, 24, & 48 hrs. Total: 1500mg base (=2500 mg salt) Hydroxychloroquine 620mg base (=800mg salt) orally immediately, followed by 310mg base (=400mg salt) orally at 6, 24 & 48 hrs. Total: 1550mg base (=2000mg salt) Primaquine 30mg base oral oncedaily for 14 days	Chloroquine 10mg base/kg orally immedia-tely, followed by 5mg base/kg orally at 6, 24, & 48 hrs. Total dose: 25mg base/kg Hydroxychloroquine 10mg base/kg orally imme-diately, followed by 5mg base/kg orally at 6, 24 & 48 hrs. Total dose: 25mg base/ kg Primaquine 30mg base orally once daily for 14 days	Chloroquine or Hydroxy-chloroquine
Chloroquine-resistant P. vivax§ (Papua New Guinea and Indonesia)	Mefloquine or Atovaquone-proguanil (Malarone) plus Primaquine	Mefloquine 648mg base (=750mg salt) orally as initial dose, followed by 456mg base (=500mg salt) orally given 6-12 hours after initial dose (total dose = 1250mg salt) Atovaquone-proguanil Adult tab = 250mg atovaquone / 100mg proguanil. 4 adult tabs orally once daily for 3 days Primaquine (as above)	Mefloquine 13.7mg base/kg (=15mg salt/ kg) orally as initial dose, followed by 9.1mg base/kg (=10mg salt//kg) orally given 6-12 hrs after initial dose (total dose = 25mg salt/kg) Atovaquone-proguanil Peds tab=62.5 mg ato-vaquone/ 25mg proguanil. All doses given oral once daily for 3 days: 5-8 kg: 2 peds tabs; 9-10kg: 3 peds tabs; 11-20 kg: 1 adult tab; 21-30 kg: 2 adult tabs; 31-40 kg: 3 adult tabs; >40kg: 4 adult tabs Primaquine (as above)	Mefloquine (only)
	B. Quinine plus one of following: Doxycycline Tetracycline plus Primaquine	Quinine¥ 542mg base (=650mg salt) orally three times daily x 3 to 7 days Doxycycline 100mg orally twice daily x 7 days Tetracycline 250mg orally four times daily x 7 days Primaquine (as above)	Quinine¥ 8.3mg base/kg (=10mg salt/kg) orally three times daily x 3 to 7 days Doxycycline 2.2mg/kg orally twice daily x 7 days Tetracycline 25mg/kg/day orally divided four times daily x 7 days Primaquine (as above)	Quinine (only
P. malariae *P. knowlesii*	Chloroquine Or Hydroxy-chloroquine	Chloroquine (as above) Hydroxychloroquine (as above)	Chloroquine (as above) Hydroxychloroquine (as above)	Chloroquine or Hydroxy-chloroquine

* Dosing as for adults. Primaquine, doxycycline, and tetracycle are contraindicated in pregnancy.

Hydroxychloroquine is a second line alternative to chloroquine.

Primaquine is used to prevent *P. vivax* and *P. ovale* relapse by eradicating hypnozoite forms that may remain dormant in liver. Because primaquine can cause hemolytic anemia in persons with G6PD deficiency, screening for G6PD deficiency is required prior to starting treatment with primaquine. Primaquine contraindicated in pregnancy given uncertain neonatal G6PD status.

To prevent relapse of *P. vivax*, primaquine should be dosed 30 mg/day for 14 days. To prevent *P. ovale* relapse, primaquine should be dosed 15 mg base/day for 14 days. Primaquine therapy should begin on same day with chloroquine.

§ For treatment of uncomplicated malaria due to chloroquine-resistant *P. vivax* there are two options (A or B) that are equally recommended. Individuals with *P. vivax* acquired outside of Papua New Guinea or Indonesia should be started on chloroquine; if patient does not respond, treatment should be changed to a chloroquine-resistant *P. vivax* regimen.

¥ For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections in Africa and South America, quinine treatment should continue for 3 days. In US quinine is encapsulated in a 324mg dose; for adult dosing 2 capsules sufficient. For pediatric dosing, if non-capsule forms not available, atovaquone-proguanil or mefloquine may be used.

Doxycycline and tetracycline are not indicated for use in children <8 years. For children <8 years with chloroquine-resistant *P. vivax*, quinine (given alone for 7 days) or mefloquine may be used. If options not available or not tolerated and if treatment benefits outweigh the risks, doxycycline or tetracycline may be given to children <8 years.