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MALARIA: A GENERAL MINIREVIEW WITH REFERENCE TO EGYPT

By

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Abstract

The majority of world's population-live in areas at risk of malaria transmission. Malaria is a serious *Anopheles*-borne disease that causes symptoms like the flu, as a high fever, chills, and muscle pain also, anemia, bloody stools, coma, convulsion, fever, headache, jaundice, nausea, sweating and vomiting. Symptoms tend to come and go in cycles. Apart from Anopheles vector, malaria could be transmitted nosocomial, blood transfusion or needle-stick injury

Some types of malaria may cause more serious damage problems to heart, lungs, kidneys, or brain. These types can be deadly. The primary factors contributing to the resurgence of malaria are the appearance of drug-resistant strains of the parasite, the spread of insecticide-resistant strains of the mosquito and the lack of licensed malaria vaccines of proven efficacy. In rare cases, people can get malaria if they come into contact with infected blood as in blood transfusion or needle-stick injury also nosocomial and congenital malaria was reported.

This is a mini-review of malaria with information on the lethal to humans, *Plasmodium falciparum*, together with other recent developments in the field.

Key words: Egypt, Malaria, Diagnosis, Treatment, Travelling, Prevention

Review, Discussion and Comments

Malaria (Alternative Names: Quartan malaria; Falciparum malaria; Biduoterian fever; Black-water fever; Tertian malaria; Plasmodium) is an important cause of fever and serious illness in returned travelers. Among nearly 7000 returned travelers with fever seen at a Geo-Sentinel clinic between 1997 &2006, for example, malaria was the most common specific etiologic diagnosis, found in 21% of cases. The relative risk of malaria is higher among returned travelers from the Sub-Saharan Africa than those from Asia or the Americas (Wilson *et al,* 2007).

Approximately 1500 cases of imported malaria are reported annually to the CDC; this is likely an underestimate given underreporting in the United States (Mali *et al,* 2008). More than half of the reported cases are due to *P. falciparum*, which causes the most severe disease; patients with *P. falciparum* may progress to life-threatening illness within hours and it is associated with widespread drug resistance. Since 1997, there has been an average of six malaria deaths per year in the United States (Bruneel *et al,* 2003). The human *Plasmodium* malaria are caused by *P. falciparum: P. vivax, P. ovale, P. malariae*, and *P. knowlesi* (Cox-Singh *et al,* 2008). 1- *P. falciparum* causes the most severe disease; patients with this form of malaria may progress to life-threatening illness within hours (Guerra *et al*, 2006). 2- *P. 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 (Kochar *et al*, 2005). 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 anopheline mosquitoes (even for brief periods) including temperate latitudes on the Korean peninsula, China, Russia, and countries in southwestern Asia such as Iran, Afghanistan, and Tajikistan. The lack of anopheline 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* (Strickland, 2000). 3- *P. ovale* malaria has been described in tropical west-

ern Africa and with rare frequency in Southeast Asia and Oceania. According to a survey performed in 1966, the only endemic areas for *P. ovale* malaria outside of Africa were the Philippine archipelago and the island of New Guinea. In a report of 15,806 blood film examinations at several sites in Indonesia between 1973 and 1989, 34 infections due to *P. ovale* were identified; the frequency of *P. ovale* relative to *P. falciparum* and *P. vivax* was <1:1000 (Hay *et al,* 2004). 4- *P. malariae* tends to occur with relatively low prevalence in isolated pockets throughout the tropics (Mueller *et al,* 2007). 5- *P. knowlesi* is an emerging human pathogen initially recognized in 2004, although the first human case was described in 1965 (Chin *et al,* 1965). Malaria due to *P. knowlesi* was described in Malaysian Borneo; cases have also been reported 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 (Kantele and Jokiranta, 2011). *P. knowlesi* replicated every 24 h in the human host and hence, causes quotidian malaria. It causes a wide spectrum of clinical manifestations and sometimes can cause fatal illness, and chloroquine is effective in the treatment of uncomplicated infection (Vadivelan and Dutta, 2014).

Humans living or traveling in all of these regions (e.g., within range of distribution of *A. leucosphyrus* vector), especially those living in proximity to macaques, may be considered at risk of infection by *P. knowlesi* (Luchavez *et al,* 2008). It appears to be a threat not only to the local population in Malaysia. Tourism resulted in increasing cases in Europe, America, and Oceania (Müller and Schlagenhauf, 2014) and to Germany from Thailand (Orth *et al*, 2013).

Clinical manifestations: Malaria should be suspected in the setting of any febrile illness after exposure to a region where malaria is endemic? (Wilson *et al,* 2007). Symptoms and signs of uncomplicated malaria may also include tachycardia, tachypnea, chills, malaise, fatigue, diaphoresis, headache, cough, anorexia, nausea, vomiting, abdominal pain, diarrhea, arthralgias and myalgias. The physical findings may include jaundice, splenomegaly and/or hepatomegaly.

Moreover, manifestations of severe disease should prompt consideration of mixed infection with *P. falciparum.* These include hemodynamic instability, pulmonary edema, severe anemia, massive intravascular hemolysis, coagulopathy, hypoglycemia, metabolic acidosis, renal failure, hepatic dysfunction, altered mental status, focal neurological deficits and seizures. Febrile seizures are not a sign of severe malaria; a single seizure in the setting of a high temperature requires aggressive fever management with anti-pyretics to distinguish a febrile seizure from seizures associated with central nervous system complications of malaria (Ramharter *et al*, 2005)

Prevention efforts should be aimed at all forms of malaria. In addition to *P. falciparum*, other *Plasmodium* species that cause human malaria include *P. vivax, P. ovale, P. malariae* and *P. knowlesi*. These forms of malaria usually cause febrile illness but less commonly result in severe disease and are rarely fatal, although deaths have been reported in the setting of *P. vivax* and *P. knowlesi* infections (Cox-Singh *et al,* 2008).

In general, most chemoprophylaxis regimens are designed to prevent primary attacks of malaria but may not prevent the later relapses that can occur with *P. vivax* and *P. ovale*.

Most travelers who develop malaria do not adhere to an effective chemoprophylactic drug regimen, as many travelers frequently fail to use personal protection measures for mosquito bite prevention (Svenson *et al*, 1995).

Risk assessment: The risk of malaria transmission depends on a variety of factors including the geographic region visited and the type of traveler (Freedman, 2008).

Destination: In addition to the geographic region visited, the risk of malaria transmission depends upon the type of accommodation (e.g., open air, tented, air conditioned or screened), the season (rainy versus dry), the elevation, and the duration of exposure.

Geographic risk assessment for malaria requires detailed review of the planned itinerary together with the most recent CDC guidelines and advisories. Listings of regions where malaria transmission occurs, the presence of the antimalarial drug resistance, and recommended chemoprophylaxis for specific destination are available in the CDC publication "Health Information for International Travel" (also known as the Yellow Book), which may be accessed online (CDC, 2008a).

Travelers: The important risk groups include travelers born in regions with endemic malaria that relocate outside the endemic area but subsequently return to visit friends and relatives (known as VFRs), pregnant women and military personnel.

VFR travelers are at greatest risk for malaria infection; this group includes individuals born in regions with endemic malaria who have emigrated outside these regions, as well as the subsequent family generation of children born outside endemic areas. VFRs pose unique challenges for malaria prevention since their acquired immunity afforded some degree of protection against malaria while they resided in the endemic area, although such immunity wanes outside endemic regions (Askling *et al*, 2005). In addition, such individuals may have difficulty seeking or accessing preventive services, may receive incorrect information regarding appropriate prophylaxis measures, and may not appreciate the risk or severity of infection once their immunity has waned (Angell and Cetron, 2005).

Pregnant women are also an important risk group, as malaria can be a life threatening infection for both mother and fetus. Risk of stillbirth, spontaneous abortion, and other adverse pregnancy outcomes is increased in the setting of malaria, and pregnant travelers should be advised to defer travel until after delivery whenever feasible.

Military personnel represent another important risk group; these individuals may have inadequate protection from mosquito bites given prolonged periods of nighttime exposure to biting *Anopheles* mosquitoes with accommodations that have inadequate screens or bed-nets (Ciminera and Brundage, 2007).

Counseling: Travelers to malarious areas should understand that their planned itinerary puts them at risk for malaria, a serious infection that can be fatal.

Prevention measures include avoiding mosquito bites and adhering to the antimalarial chemoprophylaxis. However, travelers should also understand that no chemoprophylaxis regimen guarantees complete protection and that fever during or after travel is a medical emergency requiring urgent medical attention. Other symptoms may include headache, myalgia, cough, nausea, abdominal pain, vomiting, and diarrhea.

Travelers should be counseled that their travel history is an important clue to bring to the attention of the health care provider in the first year following exposure. Because most chemoprophylactic agents do not eradicate the dormant hypnozoites of *P. vivax* and *P. ovale* capable of causing relapsing malaria (with the exception of primaquine), infection with these species may present months following exposure in spite of full adherence to chemoprophylaxis. Among imported malaria cases in the United States in 2006, no cases of *P. falciparum* occurred more than six months following travel, although 18.1% of *P. vivax* cases occurred after this interval. However, in semi-immune individuals born in endemic areas, *P. falciparum* may present up to three years following travel (Schwartz *et al,* 2003). Travelers planning prolonged visits to endemic areas must continue prophylaxis during their stay. Local laboratories in developing regions may have high rates of false-positive malaria

diagnoses; travelers who become ill should be advised to seek expert advice concerning malaria diagnosis and therapy (Keystone, 2004).

In such cases the chemoprophylactic regimen should be continued together with treatment offered locally, unless there are significant drug-drug interactions (such as mefloquine with halofantrine). If the initial evaluation demonstrates negative blood films, thick and thin blood films should be repeated twice (12 to 24 hours apart).

Pregnant women are an important risk group, as malaria can be a life threatening infection for both mother and fetus. Risk of stillbirth, spontaneous abortion, and other adverse pregnancy outcomes is increased in the setting of malaria, and pregnant travelers should be advised to defer travel until after delivery whenever feasible.

Mosquito Bite Prevention: 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 (permethrin) Staying in well-screened or air-conditioned rooms (Fradin and Day, 2002).

Insect repellents recommended by the CDC 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) had comparable efficacy for protection against malaria vectors up to eight hours after application (Frances *et al*. 2004). The highest concentration of picaridin sold in the US is 15%, and there is not sufficient data to support adequate protection against *Anopheles* at this concentration.

In addition to insect repellants applied to skin, fabric may be treated with permethrin or other residual insecticides. Permethrin is a synthetic compound that causes nervous system toxicity to insects with low toxicity for humans (Kimani *et al,* 2006). It is available in outdoor supply stores as an aerosol clothing spray (Permanente Repellent).

Clothing and bed netting treated with permethrin effectively repel mosquitoes for more than one week even with washing and field use. Standard nets dipped in permethrin proved effective for three washes whereas newer formulations can withstand 20 washes (Fradin, 1998).

Long lasting insecticide impregnated nets can remain effective as long as three years. Use of such nets is very effective for reducing the risk of malaria infection and travelers to the endemic areas with accommodations lacking screens or air conditioning (such as VFRs or hikers) should sleep under insecticide treated nets (Nevill *et al,* 1996).

Transmission other than by *Anopheles* spp.: Nosocomial or needle-stick injury: Cannon *et al*. (1972) reported transmission of *P. falciparum via* Non-intact skin to Health care worker. Börsch *et al*. (1982) reported Malaria transmission from patient to nurse to non-intact skin by needle-stick injury and Freedman (1987) in South Africa reported two nurses who acquired malaria by needle-stick injury. Guerrero *et al*. (1983) and Nahlen *et al*. (1991) and (Mungai *et al*, 2001) in USA reported malaria transmission by blood transfusion. Herwaldt and Juranek (1993) in USA reported laboratory-acquired malaria, leishmaniasis, trypanosomiasis, and toxoplasmosis by needle-stick injury and *P. cynomolgi* transmission to laboratory researcher's normal skin by needle-stick injury. Piro *et al*. (2001) in Libya described two cases of malaria occurring in a malaria-free zone in two patients, two weeks after a case of *P. falciparum*, acquired in Burkina Faso,

had been admitted to the same ward. After reviewing the techniques used by nursing staff, concluded that transmission occurred via gloves contamination after manipulation of venous cannulas and drip lines of patient with Burkina Faso-acquired malaria that was not discarded before manipulating intravenous lines of the other two patients. Nosocomial transmission of unusual and potentially life-threatening infections should be taken into consideration in those settings where compliance with universal precautions is not rigorous. Alweis *et al*. (2004) in USA reported a nurse who developed *falciparum* malaria after a needle-stick injury from a patient with proved malignant malaria. Three days prior to her diagnosis, she cared for another patient, who subsequently developed falciparum malaria. That patient's parasite isolate genetically matched the nurse's isolate by two independent DNA fingerprinting techniques. They believed that a nurse who had acquired falciparum malaria via needle-stick subsequently transmitted malaria to another patient via a break in standard precautions.

Chemoprophylaxis: Individual itineraries should be reviewed together with the update guidelines and advisories to determine the appropriate approach to chemoprophylaxis. Listings of regions with risk for the malaria transmission, the presence of the antimalarial drug resistance, and recommended chemoprophylaxis were reported (CDC, 2008a).

Drug Mechanisms: There are three major categories of drugs for prevention of malaria, which target liver active tissue schizonts. Atovaquone/ proguanil proved active against liver stages of *P. falciparum*.

Hypnozoiticide- Hypnozoites are a quiescent stage in the liver that exists only in the setting of *P. vivax* and *P. ovale* infection. This liver stage does not cause clinical symptoms, but with reactivation and release into the circulation, late-onset or relapsed disease can occur up to many months after initial infection.

Primaquine is active against the quiescent hypnozoites of *P. vivax* and *P. ovale*. This class of drugs targets the asexual blood stages of the parasite: chloroquine, mefloquine, doxycycline, atovaquone/proguanil and primaquine. As the first three agents act on blood parasites following release from the initial maturation phase in the liver, these drugs must be continued for four weeks following exposure to eradicate parasites released from the liver.

Primaquine has schizonticidal activity against the tissue stages of all species and blood stages of the non-*falciparum* species, but lacks blood schizonticidal activity against *P. falciparum*. Since atovaquone/ proguanil and primaquine act as both blood and tissue schizonticides, they interfere with development of actively replicating parasites in the liver, so can be discontinued one week after the end of exposure.

Drug Resistance: Antimalarial selection should include the considerations of regions with malarial drug resistance (Wellems and Plowe, 2001). Individual itineraries should be reviewed together with the most recent guidelines and advisories.

The resistance of *P. falciparum* to chloroquine is widespread; regions with chloroquine-resistant and chloroquine-sensitive malaria are summarized below: Chloroquine-resistant *P. falciparum* (CRPF) is widespread in endemic areas of Africa, Asia and Oceania. Chloroquine-sensitive *P. falciparum* exists in Mexico, the Caribbean, Central America west and north of the Panama Canal, and parts of North Africa, the Middle East, and China. *P. falciparum* strains resistant to chloroquine, mefloquine and sulfonamides are rare, but are prevalent in the regions of Thailand bordering Burma (Myanmar) and Cambodia (e.g., eastern provinces of Myanmar and western provinces of Cambodia, including Siem Reap), and in parts of China, Laos, and Vietnam. Chloroquine-resistant *P. vivax* is widespread in Indonesian Papua and Papua New Guinea (Baird *et al*, 1996).

Regimens: Chemoprophylaxis agents vary with respect to cost, adverse effects, and dosing schedule. Reviewing these items during the travel visit is important for facilitating adherence. In 2006, 94% of the US travelers with malaria took no chemoprophylaxis, took an ineffective drug, or took an appropriate drug incorrectly (Chen *et al*, 2008).

Antimalarial therapy should be started prior to travel, continued regularly during exposure, and for a period of time following departure from the endemic area. A prescription for the full supply of medication should be written and filled prior to departure; the sale of counterfeit and poor quality antimalarials is an increasing problem in Asia and Africa. Travelers should understand the importance of careful adherence to the chemoprophylaxis regimen, even though no chemoprophylaxis regimen guarantees complete protection.

1-Atovaquone-proguanil: Atovaquone acts synergistically with proguanil against chloroquine-sensitive and chloroquine-resistant *P. falciparum*, as well as the other malaria species that cause human malaria. Its efficacy is equivalent to that of mefloquine. Atovaquone-proguanil does not prevent hypnozoite formation by *P. vivax* or *P. ovale*; in areas with high rates of infection due to these species, presumptive anti-relapse therapy with primaquine may be necessary to prevent relapse for persons who had been to those areas for extended periods of time (Boggild *et al,* 2007). Atovaquone-proguanil is administered daily beginning two days prior to exposure, during exposure, and for one week following exposure. Drug is well tolerated, with excellent profiles of safety and efficacy (van Riemsdijk *et al,* 2002). Side effects include gastrointestinal upset, insomnia, headache, rash and mouth ulcers.

Atovaquone-proguanil is contraindicated in patients with creatinine clearance <30 mL per minute and it is not recommended for use in pregnant women due to insufficient safety data (McKeage and Scott, 2003).

2-Mefloquine: 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 140,000 travelers to East Africa, the prophylactic efficacy of mefloquine was 91%.

Mefloquine is not effective for prevention of malaria due to mefloquine-resistant *P. falciparum*, which is found along the Thailand-Cambodian border region, and parts of China, Burma (Myanmar) and Vietnam. In addition, mefloquine does not prevent the development of residual hepatic hypnozoite forms of *P. vivax* or *P. ovale* malaria. For those with extended exposure to areas with high rates of infection due to these species, presumptive anti-relapse therapy with primaquine may be necessary to prevent relapse. Mefloquine is administered weekly beginning at least two weeks prior to exposure, during exposure, and for four weeks following exposure.

Some travelers experience adverse effects from mefloquine; most are mild, self-limited, and do not require drug discontinuation. The commonest adverse effects are gastrointestinal upset, lightheadedness, headache, difficulty concentrating, mood swings, strange dreams, and about 5% of them experience disabling neuropsychiatric adverse effects requiring discontinuation of the drug. These include anxiety, depression, nightmares, paranoid ideation and dizziness. Travelers about 1/10,000 experienced severe neuropsychiatric reactions; as seizures and psychosis. Adverse effects are the commonest among women and less among children. Most adverse ones requiring mefloquine discontinuation occur within first three doses. So, some favor start mefloquine four weeks prior to travel to determine drug tolerance.

Contraindications to mefloquine include known hypersensitivity to the drug, a history of seizures or major psychiatric disorder, and a recent history of depression or anxiety. Development of psychiatric symptoms (such as depression, anxiety, restlessness or confu-

sion) while taking mefloquine should be viewed as a possible prelude to other events; in such circumstances it is advisable to stop the drug immediately and switch to a different prophylaxis agent. Mefloquine has also been associated with sinus bradycardia and QT interval prolongation; therefore, it should be used with caution in patients with cardiac conduction disorders.

For pregnant patients who cannot avoid travel to areas with chloroquine-resistant *P. falciparum*, limited data suggest that mefloquine may be safely administered during the second and third trimesters, and can probably also be administered during the first trimester (Nosten *et al*, 1994).

3- Doxycycline: Doxycycline has activity against chloroquine-sensitive and chloroquine-resistant *P. falciparum*, as well as the other malaria species that cause human malaria (Soto *et al*. 1998). Comparative trials have demonstrated equivalent efficacy of doxycycline with mefloquine (e.g., 93 to 99%). Doxycycline can provide some protection against infection with some rickettsial infections (e.g., scrub typhus) and *Leptospira* spp. However, doxycycline does not prevent the development of residual hepatic hypnozoite forms of *P. vivax* or P. *ovale* malaria. Thus, for those with extended exposure to areas with high rates of infection due to these species, presumptive anti-relapse therapy with primaquine may be necessary to prevent relapse.

Doxycycline is administered daily beginning one to two days prior to exposure, daily during exposure, and daily for four weeks following exposure. Noncompliance with this daily regimen is an important reason for doxycycline prophylaxis failure (Wallace *et al.* 1996). Doxycycline is usually well tolerated, but has been associated with gastrointestinal upset; less commonly, ultraviolet photosensitivity, *Candida vaginitis,* and rare cases of esophageal ulceration may also occur. The drug should be taken with fluids and food; it should not be administered immediately before lying down. Sunscreen should be applied liberally for the duration of prophylaxis. It is advisable to offer women antifungal self-treatment for management of *C. vaginitis* (e.g., fluconazole). Doxycycline is contraindicated in pregnant women and in children <8 years of age (Morris and Davis, 2000).

4-Chloroquine: Chloroquine may be used for prophylaxis for individuals traveling to malarious areas without chloroquine resistance. Chloroquine has activity against all Plasmodial species causing human malaria with the exception of chloroquine-resistant *P. falciparum* strains and uncommon strains of *P.* vivax in Oceania and Asia. Chloroquine did not prevent residual hepatic hypnozoite forms of *P. vivax* or *P. ovale*. Thus, for those with extended exposure to areas with high rates of infection due to these species, presumptive anti-relapse therapy with primaquine is a must to prevent relapse. The formulations include chloroquine phosphate and hydroxychloroquine (CDC, 2008b). Chloroquine is administered once weekly starting one week prior to exposure, once weekly while in the malaria endemic area, and then once weekly for four weeks following exposure. Apart from its bitter taste, chloroquine is usually well tolerated. Minor side effects include gastrointestinal disturbances, dizziness, blurred vision, and headache; gastrointestinal problems may be alleviated by taking the drug with food. It has been associated with triggering flares of psoriasis and pruritis, although serious side effects are rare. Pruritus occurs in up to 25 % of blacks due to concentration of the drug in skin; this is not an allergic reaction. Retinal injury, which can occur when high doses of chloroquine are used to treat rheumatoid arthritis, does not occur with the weekly dosages used for malaria prevention and safe for use in pregnancy (Salako, 1984).

5- Primaquine: Primaquine has activity against many stages of the malaria parasite including hypnozoites, tissue schizonts, gametocytes, and asexual blood stages of *P. vivax* (Baird *et al.* 2003) in preventing re-

lapses from the hypnozoite forms of *P. vivax* and *P. ovale*; it also has activity against *P. falciparum,* including chloroquine-resistant species. The efficacy of primaquine against *P. falciparum* and *P. vivax* is 74 to 95% and 85 to 92%, respectively. Primaquine may be used either as presumptive anti-relapse therapy (PART) or as primary prophylaxis. Primaquine primary prophylaxis is appropriate for travelers to regions where the principal endemic species is *P. vivax* (such as Mexico and Central America). Primaquine is administered daily beginning one to two days prior to exposure, once daily during exposure, and daily for seven days following exposure.

Primaquine can cause hemolytic anemia in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Therefore, a G6PD level must be determined prior to administration of this drug and patients should receive primaquine only if G6PD deficiency has been excluded. Primaquine may also cause gastro-intestinal upset that can be minimized if taken with food. Primaquine is contraindicated in pregnancy and breastfeeding (Hill *et al,* 2006).

Relapse Prevention: Late-onset or relapsed disease due to reactivation of hypnozoites can occur up to many months after initial infection. Hypnozoites are a quiescent stage in the liver that exists only in the setting of *P. vivax* and *P. ovale* infection. According to CDC (2006) surveillance data, 220 travelers who took appropriate chemoprophylaxis were diagnosed with malaria; among the 80 cases of *P. vivax* or *P. ovale* in this group, 51% developed symptoms >45 days after arrival in the United States. Hepatic stages cause no fever symptoms and one does not need to have had a primary clinical episode of malaria in order to have a relapse.

Use of primaquine for presumptive anti-relapse therapy (PART; the term terminal prophylaxis has also been used in the literature) is appropriate for travelers to regions where there is substantial risk of *P. vivax* or *P. ovale* transmission, even if *P. falciparum* is the predominant endemic species. This is especially appropriate for travelers with prolonged stays where *P. vivax* or *P. ovale* are present.

In addition to administration of an agent with activity against blood stage parasites prior to, during, and following exposure (such as atovaquone-proguanil, mefloquine or doxycycline), primaquine is added for activity against liver hypnozoites which can cause disease after the completion of the primary chemoprophylaxis regimen (Galappaththy *et al*. 2007).

Following departure from an endemic area, primaquine should be administered for 14 days together with the remainder of the primary prophylaxis regimen. If the primary prophylaxis regimen has already been completed, a course of primaquine is still beneficial for prevention of relapse.

Pregnant Travelers: Malaria can be a life threatening infection for both mother and fetus. Risk of stillbirth, spontaneous abortion, and other adverse pregnancy outcomes is increased in the setting of malaria, and pregnant travelers should be advised to defer travel until after delivery whenever feasible (Lindsay *et al,* 2000).

For pregnant women who cannot defer travel to regions where chloroquine-sensitive malaria is present, mosquito avoidance is a must in conjunction with chemoprophylaxis with chloroquine and Mefloquine is also acceptable (Smoak *et al*. 1997).

For pregnant women who cannot defer travel to regions where chloroquine-resistant malaria is present, mosquito avoidance measures should be used in conjunction with the chemoprophylaxis using mefloquine (Okeyeh *et al,* 1996).

Limited data suggest that mefloquine may be safely administered during the second and third trimesters, and can probably also be administered during the first trimester. Safety data on atovaquone-proguanil in pregnancy are limited, so should be avoided. The doxycycline should not be administered during pregnancy because of potential adverse effects to the fetus including dysplasia

and inhibition of bone growth and dental discoloration. Primaquine should not be administered during pregnancy given the potential possibility for fetal G6PD deficiency (Vanhauwere *et al*, 1998).

Drug interactions: The traveler's medication history should be reviewed in detail with consideration for potential drug-drug interactions. Some relatively common drugs with important interactions include: Warfarin: Atovaquone/proguanil may diminish the metabolism of warfarin. Coagulation parameters should be monitored closely if these drugs are used together, and warfarin dosing may need to be reduced. Antiarrhythmic agents: these drugs should be used with caution in the setting of mefloquine administration, which has been associated with been associated with sinus bradycardia and QT interval prolongation. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors: these agents may diminish metabolism of antimalarials and lead to potential interaction that may require the close monitoring, alteration of drug dosage or timing of administration (Khoo *et al*. 2005).

In light of limited data, doxycycline seems to have the least potential for drug-drug interactions with HIV drugs. Immunosuppressive medications: chloroquine may increase cyclosporine levels and both doxycycline and mefloquine may increase levels of cyclosporine and tacrolimus. Atovaquone-proguanil does not have known interactions with these medications (Kotton *et al,* 2005).

Suggested approach: Selection of chemoprophylaxis must be tailored to individual itineraries and circumstances. For patients traveling to several destinations with different types of malaria risk, it may be simplest to select a single agent that will be effective for the entire duration of exposure.

For travelers to destinations where malaria cases occur only sporadically and risk to travelers is very low, mosquito avoidance measures should be used; no chemoprophylaxis is needed. For travelers to destinations where chloroquine-resistant *P. falciparum* is present, mosquito avoidance measures must be used in conjunction with chemoprophylaxis.

The options include atovaquone/proguanil, mefloquine and doxycycline; all three agents are highly efficacious for prevention of malaria. Comparative studies among travelers taking mefloquine or atovaquone/proguanil have demonstrated fewer side effects experienced among recipients of atovaquone/ proguanil, although this agent is more costly (Camus *et al*. 2004).

The short term travelers may prefer the shorter course of the atovaquone /proguanil, while long term travelers may prefer the convenience of weekly mefloquine. The doxycycline requires a prolonged course, must be taken daily, and causes sun sensitization, although it is the least expensive of these agents.

For travelers to destinations where chloroquine-sensitive *P. falciparum* malaria is present, mosquito avoidance is a must in conjunction with chemoprophylaxis.

Chloroquine may be used, although short term travelers may prefer shorter atovaquone /proguanil course. Mefloquine and doxycycline are also effective agents. For travelers to Mexico and Central America where *P. vivax* are dominant, mosquito avoi-dance is a must in conjunction with chemoprophylaxis. Primaquine may be used in absence of G6PD deficiency; chloroquine is also effective. Short term travelers prefer shorter atovaquone/proguanil course. Mefloquine and doxycycline are also effective agents.

For travelers to *P. falciparum* strains resistant to chloroquine, mefloquine, and sulfonamides are present as in malaria-endemic regions of Thailand bordering Burma (Myanmar) and Cambodia and western provinces of Cambodia, China, Laos, and Vietnam, mosquito avoidance is a must in conjunction with chemoprophylaxis. Options include atovaquone/ proguanil or doxycycline

. In Egypt, the last focus of malaria was in El-Fayoum which became free from transmission of malaria since 1998 and prepared

to be certificated as free of malaria. There were few annual imported malaria cases since the year 1998. As to situation in Egypt; all detected cases were imported (WHO, 2012a). The outbreak of *P. falciparum* and *P. vivax* in southern part at Aswan Governorate at May 2014 strongly supported the fact that malaria is reemerging (Kenawy, 2015). There are many factors contribute to the re-emergence of malaria. Such factors include infection of local Anopheline spp. by imported cases, continuous movement of populations between Aswan Governorate and Sudan as well as the influx of large population from Africa and Asia to Egypt for educational and religious purposes. Another risk factor was the environmental changes brought by water-sources development projects as Toshka (Shoukry and Morsy, 2011) and El Salam canal (Hassan *et al*, 2003). El Bahnasawy *et al.* (2011) recorded *An. multicolor, An. Sergentii* and *An. algeriensis* in Toshka District, and added that the endemicity of Chloroquine resistant *P. falciparum* on the Egyptian-Sudanese border pave the way for malignant malaria transmission. El Bahnasawy *et al,* (2014) stated that travelling to different climates, cultures and environments abroad are exposed to tropical infectious diseases and health risks. They added that a rural health nursing has long been considered a subspecialty within public health nursing, albeit one that required the nurse to be a generalist, and applied an educational program for nursing staff on selected infectious disease disasters, which vectors are encountered at Egyptian Sudanese borders.

The imported malaria refers to infections acquired outside and brought into a national territory (WHO, 2012b). The origin of imported cases can be traced to a known malarious area outside the country to which the case has travelled (WHO, 2012c). Only *An. pharoensis* and *An. sergenti* are the proven vectors in Egypt. *An. pharoensis* is mainly responsible for *Plasmodium vivax* transmission while, *An. sergenti* is responsible for the *P. falcipaum* transmission in El Fayoum (Kenawy, 1988). Also, *An. multicolor* is suspected as a vector (Gad *et al*, 1964; Zahar, 1974; Kenawy *et al*, 1986). *An. sergenti* is the oasis vector or desert malaria vector due to its distribution across the Saharan belt in northern Africa into the Middle East, and its ability to cope with extreme climate condition (Sinka *et al*, 2010). *An. sergenti* is an important vector of malaria in the oases and in Al Fayoum (Farid, 1956; Morsy *et al*, 1995a,b).

Moreover, el Said *et al*. (1986) in 2 neighboring villages in Al Faiyum Governorate monitored Anopheles populations over a year, to study factors causing differences in malaria prevalence. Both villages contained: *An. pharoensis, An. sergentii, An. multicolor* and *An. tenebrosus*. They reported that *An. pharoensis* and *An. sergentii* were the dominant species in Abheet with seasonal biting activity extending from May to December, reaching a peak in November. They added that *An. pharoensis and An. sergentii* were both incriminated as malaria vectors based upon their seasonal abundance and the finding of sporozoite positive specimens during the peak malaria season.

Bassiouny *et al*. (1999) in Al-Fayoum carried out a one-year longitudinal entomological study in Kafr Fazara village, Sinnuris District. They found *A. sergenti* the most prevalent species followed by *A. multicolor* and the least one was *A. pharoensis*. They concluded that the mean monthly temperature only and not relative humidity nor wind speed had a significant effect on larvae abundance, and that *P. falciparum* transmission season extended to more than eight months a year which could explain the persistence of malaria up there.

Mostafa and Allam (2001) tested Insecticides; malathion, fenitrothion, temephos, diazinon, bromophos and fenthion from organophosphorous group and deltamethrin, permethrin and cypermethrin from synthetic pyrethroid group while propoxur was from carbamate group, against adult and larvae of *A. pharoensis* and *C. pipiens* mosquitoes

from Al-Fayium Governorate. They found that. *A. pharoensis* larvae were resistant to fenitrothion and susceptible to other insecticides, while adults were susceptible to malathion, deltamethrin, fenitrothion and premethrin.

Zaher *et al*. (2007) reported 16 malaria cases in Almaza Military Fever Hospital. They were 9 imported pilgrims (56.2%) of *P. falciparum* and 7 cases (43.8%) acquired *P. vivax* locally (October 2003 to July 2004). They were all treated successfully by chloroquine. Fuller *et al*. (2012) stated that *A. arabiensis* is a particularly opportunistic feeder and efficient vector of *P. falciparum* in Africa and might invade areas outside its normal range, including areas separated by expanses of barren desert. They demonstrated how spatial models could project future irrigated cropland and potential, new suitable habitat for vectors such as *A. arabiensis* and how land change and species distribution models might be linked to project potential changes in vector habitat distribution and invasion potential. They added that while gaps between potential habitat patches remained large in the Green Nile scenario, the models reveal large areas of future habitat connectivity that may facilitate the reinvasion of *A. arabiensis* from Sudan into Upper Egypt.

El-Bahnasawy *et al.* (2010) evaluated the clinical and the parasitic status of malaria as a cause of fever among patients admitted to the Military Fever Hospitals. Thirty six patients were included twenty already diagnosed as malarial patients, who were recruited from Peace Keeping Mission Forces in Africa and sixteen cases presented with prolonged fever coming from different locations in Egypt. Wassim (2014) reported by the secondary structure and sequence of ITS2-rDNA *An. pharoensis* proved to an important vector all over Egypt, especially in the Delta, *An. sergenti* the primary vector in the Western Desert Oases, *An. multicolor* in Al-Fayoum, *An. stephensi* in the Red Sea Coast, and *An. superpictus* in Sinai.

Dahesh and Mostafa (2015) reevaluated malaria in Al-Fayoum reported that out of 2044 examined persons, 14 (0.68%) were passive cases i.e. attending themselves to El-Fayoum malaria units after their return from Sudan. Microscopic examination of their stained thick films obtained from MOH&P shows that 9 (64.2%) out of passive cases were positive 3 of them are *P. falciparum* (33.3%) and the rest *P. vivax* 6(66.7%) The species formulas of *P. falciparum* and *P. vivax* were 33.3% and 66.7% respectively. Concerning the density class, only one vivax case was of low density class while the other cases were of high density class. All positive cases were males, imported from Sudan and most of them were merchants having trade activities in Sudan. All examined persons during active case detection ACD (1551) and neighborhood of detected cases NOD (479) were malaria negative by rapid diagnostic tests. The areas recording the highest number of imported cases were Abu Shanap, Aboxa and Kafr Aboud but none was detected. In Al Nazla *A. sergeni* and *A. multicolor* larvae were detected, but none imported case or travel to Sudan. If the situation is reversed i.e. an imported case inhabit Al-Nazla, re-emergence of local malaria may start. They added that situation of Kafr Fazara changed by using fine sand instead of clay in manufacturing red brick after prevention excavation of land. Neither imported cases nor new larvae were recorded. They recommended annual larvae surveillance, and the indoor screening to avoid adults and treating bednet or walls to reduce indoors mosquitoes.

Conclusion

Imported malaria is a health problem and needs continuous monitoring as many clinicians are not aware of it. *P. knowlesi* in Malaysia extended abroad to Europe and America. Travellers back from the known endemic areas must be examined. Nosocomial or needle-stick transmission is documented.

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