Krzysztof Korzeniewski[1], Katarzyna Pieruń[2]

MALARIA - A DISEASE OF TRAVELLERS

MALARIA – CHOROBA OSÓB PODRÓŻUJĄCYCH

[1] Zakład Epidemiologii i Medycyny Tropikalnej Wojskowego Instytutu Medycznego w Warszawie
[2] Oddział Chorób Zakaźnych Wojewódzkiego Szpitala Specjalistycznego we Wrocławiu

STRESZCZENIE

Na całym świecie z każdym rokiem wzrasta liczba podróżujących do krajów strefy klimatu gorącego w Azji, Afryce i Ameryce Południowej. Cele podróży są bardzo zróżnicowane, od biznesowych po turystyczne, których jest zdecydowanie najwięcej. Turyści coraz częściej podróżują do miejsc charakteryzujących się ekspozycją patogenów chorób transmisyjnych, przenoszonych drogą pokarmową, oddechową i płciową. Chorobą przenoszoną przez owady, będącą częstym problemem zdrowotnym zarówno lokalnej populacji, jak i ludności napływowej, jest malaria. W rejonach endemicznego występowania zimnicy żyje ponad 40% ludności świata. Kraje wysoko rozwinięte Ameryki Północnej i Europy są z reguły wolne od endemicznych ognisk choroby, niemniej jednak obserwuje się tysiące przypadków zarażeń importowanych. Również w Polsce sporadycznie notowane są zachorowania na malarię, przywleczone przez turystów powracających z Afryki, Azji, Ameryki Południowej, Australii i Oceanii. Liczba zachorowań jest uzależniona od miejsca pobytu oraz od przyjmowania bądź odrzucenia chemioprofilaktyki przeciwmalarycznej. W pracy przedstawiono ogólne informacje na temat epidemiologii, patogenezy, obrazu klinicznego i diagnostyki malarii. Szczególną uwagę zwrócono na standardy leczenia i chemioprofilaktyki choroby, które zmieniają się stosunkowo szybko, co jest związane głównie z narastającą opornością zarodźców malarii na stosowane leki.

SŁOWA KLUCZOWE*: malaria, leczenie, chemioprofilaktyka*

ABSTRACT

The number of people travelling to regions with hot climate such as Asia, Africa and South America increases steadily every year. The reason for travel varies greatly, from business trips to tourist excursions, the latter definitely prevailing. There has been an increase in travel to destinations where exposure to vector-borne, food- and water-borne, air-borne or sexually transmitted pathogens is common. As one of vector-borne diseases, malaria poses as a serious health hazard to local as well as immigrant populations. Over 40% of the world's inhabitants live in malaria-endemic regions. Although highly developed countries of North America and Europe are generally free from endemic malaria foci, numerous cases of imported infections are observed. Some cases of malaria are also reported in Poland, they are usually brought by persons returning from tropical regions in Africa, Asia, South America, Australia and Oceania. The number of cases depends on the destination as well as on the use or rejection of chemoprophylaxis. The article provides general information on epidemiology, pathogenesis, clinical manifestation and diagnosis of malaria. Emphasis has been put on treatment as well as on chemoprophylaxis of the disease, which are changing relatively quickly, what is mainly related to increasing *Plasmodium* resistance to applied medicines.

KEY WORDS: *malaria, treatment, chemoprophylaxis*

INTRODUCTION

Approximately 2.8 billion people, representing over 40% of the world's population, live in malaria-endemic areas. Each year 300 to 500 million people fall ill with malaria. An estimated 2-3 millions die, including 1 million children under five years of age (1). *Plasmodium falciparum* and *P. vivax* account for 80-95% of all malaria cases worldwide. In highly developed countries (North America, Western Europe) approximately 10,000 cases imported from malaria-affected areas, mostly Sub-Saharan Africa and South-East Asia, are registered each year (2). In Poland, approximately 20-30 individuals, mainly tourists returning from endemic areas, are treated for malaria every year (3). Sporadic cases of malaria have been known to be reported within the vicinity of airports or harbours in malaria-free countries. The disease vectors (mosquitoes) being brought to moderate climate zone on ships or aircrafts (4).

ETIOLOGY OF MALARIA

Malaria is a protozoan disease caused in humans by five species of the *Plasmodium* genus: *P. falciparum*, *P. vivax, P. malariae, P. ovale* and *P. knowlesi*. Although transmission and infection with *P. knowlesi* is mainly observed in animals, a number of human cases have been identified recently in South-East Asia. Yet so far, no evidence of man-to-man transmission of *Plasmodium knowlesi* has been found and the species is considered enzootic (5). Malaria in humans is caused by a bite from an infective female mosquito (introducing invasive *Plasmodium* forms into the bloodstream), through transfusion of blood containing trophozoites or schizonts, or vertically, from infected mother to a child. *Plasmodium* is a protozoan parasite colonizing human liver and red blood cells (6).

Disease vector. Malaria is transmitted through the bites of an infective female of the genus *Anopheles.* Disease vectors in malaria-endemic regions are observed at the altitude of up to 2000-2200 meters above sea level (with the exception of certain malaria-prone areas in Afghanistan, Pakistan, Bolivia and Ethiopia, where cases of the disease are observed at higher altitudes). The life cycle of an *Anopheles* mosquito is strongly dependent on climate conditions; in temperatures above 30^0C the full reproductive cycle lasts 7 days, whereas in temperatures below 20^0C it can extend to over three weeks. In temperatures lower than 16^0C, *Plasmodium's* reproductive cycle ceases to function due to mosquito inactivity. However, the parasites do not die and disruption is only temporary, the reproduction is resumed as soon as the conditions become favorable again. Mosquitoes, which are the vectors of malaria, need an aquatic environment to reproduce. Subsequently, larval and mature forms develop from eggs that have been laid on the water surface (7).

Plasmodium's life cycle. Sporogony, a sexual phase of *Plasmodium* life cycle, takes place in the body of a female *Anopheles* mosquito. Together with blood of an infected individual, the mosquito ingests micro- and macrogametocytes, which fuse forming a zygote. Upon maturation, a zygote acquires motility (ookinete) and can actively penetrate midgut epithelial cells where it encapsulates forming an oocyste. Inside an oocyste multiple divisions take place resulting in the production of thousands of sporozoites (invasive to humans) which subsequently migrate to mosquito salivary glands and are injected into the human bloodstream with the saliva of a feeding mosquito. Once the sexual stage of *Plasmodium* life cycle in mosquito is complete (taking 8 to 35 days, depending on species and temperature of the environment), asexual reproduction (schizogony) follows in human host. Invasive sporozoites diffuse thorough subcutaneous capillaries and reach bloodstream where they remain for approximately half an hour. A certain number of them are destroyed by human immune cells, yet the majority reaches hepatocytes where the liver stage begins, lasting from 6 to 16 days depending on species (at this stage no clinical symptoms of the disease are observed). Sporozoites invade liver cells where they undergo multiple divisions forming schizonts which, after several rounds of nuclear divisions (without cytoplasmic divisions) followed by segmentation, form thousands of merozoites. After 6 to 16 days mature schizonts rupture and merozoites are released into the bloodstream where they enter erythrocytes. In *P. vivax* and *P. ovale* infection, the predominant proportion of merozoites is released into the bloodstream, while a certain number invade subsequent hepatocytes entering into a dormant phase known as the hypnozoite. Hypnozoites can reactivate and undergo erythrocytic schizogony at a later time resulting in the relapse of malaria symptoms after several weeks or years following primary infection. In individuals infected with *P. falciparum* or *P. malariae* hepatic schizogony occurs only once. Upon entering the circulatory system merozoites invade red blood cells commencing a stage referred to as erythrocytic schizogony. At the initial stage of erythrocytic reproduction (up to 12 hours) the parasite undergoes a trophic period inside red blood cells followed by asexual replication leading to the formation of intermediary ring-like forms. Infected erythrocytes deform and schizonts emerge gradually occupying the whole inside of a red blood cell as the parasite increases in size upon maturation. Mature schizonts rupture releasing 6 to 36 merozoites (depending on species) which invade subsequent red blood cells thus initiating another cycle of erythrocytic schizogony (the cycle lasts usually 36 to 48 hours in *P. falciparum*

malaria, 48 hours in *P. vivax* and *P. ovale* malaria and 72 hours in *P. malariae* infection). After several rounds of erythrocytic schizogony a proportion of merozoites develops into micro- and macrogametocytes which are ingested by a feeding mosquito and initiate the sexual stage of *Plasmodium* replication cycle (8,9).

CLINICAL MANIFESTATIONS OF MALARIA

After an incubation period which equals extraerythrocytic schizogony and one cycle of erythrocytic schizogony (varying from 9 to 40 days depending on species), clinical symptoms appear in three typical, consecutive phases: initial feeling of cold and chills, subsequent elevation of body temperature above 40^0C, dryness of skin and mucosae, consciousness disturbance, abdominal pain associated with splenic enlargement, and final sudden drop of body temperature combined with heavy sweating. Fever paroxysms can be associated with muscle pain, headaches, nausea, vomiting, diarrhea, jaundice, hepatomegaly and spleen enlargement. During subsequent paroxysms, the severity of symptoms gradually diminish and eventually resolve after few weeks from the onset of the disease. Malaria caused by *P. falciparum* also referred to as malignant malaria is characterized by the occurrence of severe complications, with a fatality rate of 15-20%. Life-threatening clinical manifestations include coma, focal damage to the central nervous system or encephalopathy (cerebral malaria), severe anaemia, thrombocytopenic purpura and/or disseminated intravascular coagulation, respiratory distress, cardiovascular collapse, renal failure, shock and/or acidosis. Increased, cyclic breakdown of infected erythrocytes as well as alterations in their structure and antigenicity result in a distinctive fever pattern and can subsequently lead to other disturbances, such as hypersplenic syndrome (along with infected erythrocytes also a certain number of non-infected red blood cells and platelets are sequestrated). Infected and non-infected morphotic elements of the blood form complexes, which can clog capillaries leading to hypoxia and development of multiple organ failure (9,10).

LABORATORY DIAGNOSIS

Diagnosis of malaria is based upon detection of the *Plasmodium* parasite in a thick blood smear slide. The species is determined on evaluation of Giemsa-stained thin smear preserved with methanol prior to staining. Differentiation between *Plasmodium* species in light microscopy of peripheral blood specimens is based upon differences in structure and number of intracellular forms found in erythrocytes as well as on alterations in the shapes of infected red blood cells. Examination should be performed repeatedly by experienced diagnosticians in 6 to 12 hours intervals during the period of diagnosis and treatment. A single negative result should not exclude the diagnosis of malaria. Rapid immunochromatographic tests based upon the detection of *Plasmodium* antigens are increasingly used in the initial screening examinations. However, due to their low sensitivity malaria infection cannot be excluded based on negative results. In questionable cases, PCR (polymerase chain reaction) is a preferred method of confirmation of the diagnosis. Besides parasitaemia (in *P. falciparum* malaria over 2% of red blood cells are infected), anaemia, thrombocytopenia and hyperbilirubinaemia are often observed in laboratory findings (11).

TREATMENT OF MALARIA

Individuals coming from areas where malaria does not occur, who have contracted the disease in malaria-endemic regions, should in each case be treated in the same way as patients with a severe form of malaria (irrespective of the clinical course of the disease), because, unlike native populations, their immune system might be unprepared for an appropriate immunological response, which is the case in native inhabitants of Africa, Asia or South America, who suffer from malaria many times in their lives. Every case of suspected malaria among travelers coming from endemic areas requires urgent medical intervention. If a patient contracted malaria despite the use of chemoprophylaxis, a different drug should be prescribed for the treatment of the disease. If vomiting occurs within less than 30 minutes after administration of an oral antimalarial drug, the dose should be repeated; if vomiting occurs within 30-60 minutes after administration, half of the original dose should be used. Use of anti-emetics before oral antimalarial treatment is recommended (12).

In uncomplicated cases of malaria diagnosed in tourists coming from non-malaria-endemic regions the following combinations of drugs should be used:

- artemether/lumefantrine,
- dihydroartemisinin/piperaquine,
- artesunate/amodiaquine,
- artesunate/sulfadoxine-pyrimethamine,
- artesunate + mefloquine,
- artesunate + doxycycline or clindamycin,
- atovaquone/proguanil,
- quinine + doxycycline or clindamycin,
- chloroquine + primaquine (13,14).

The treatment is based mainly upon the combination of artemisine or its derivatives (artemeter, dihydroartemisinin and artesunate) and pharmaceuticals belonging to other therapeutic classes (ACT, artemisinin-based combination therapy) (tab. I).

Table I. Recommended drugs for the treatment of malaria
Tabela I. Środki farmaceutyczne stosowane w leczeniu malarii

Drug name	Dosage regimen
artemether/ lumefantrine	6 doses over 3 days: at 0, 8, 24, 36, 48 and 60 hrs dosage according to body weight (1 tablet = 20 mg artemether + 120 mg lumefantrine)
dihydroartemisinin/piperaquine	4 mg/kg dihydroartemisinin plus 18 mg/kg piperaquine once daily for 3 days (1 tablet = 40 mg dihydroartemisinin + 320 mg piperaquine)
artesunate/amodiaquine	4 mg/kg artesunate + 10 mg/kg amodiaquine once daily for 3 days (1 tablet = 25 mg/67.5 mg, 50 mg/135 mg or 100 mg/270 mg)
artesunate/ sulfadoxine-pyrimethamine	4 mg/kg artesunate once daily for 3 days (25 mg, 50 mg or 100 mg tablets) 25 mg/kg mc sulfadoxine (500 mg tablets) + 1,25 mg/kg pyrimethamine (25 mg tablets) as a single dose in the first day of treatment
artesunate + mefloquine	4 mg/kg artesunate plus 8.3 mg/kg mefloquine once daily for 3 days (50 mg artesunate + 250 mg mefloquine or 200 mg artesunate + 250 mg mefloquine tablets)
atovaquone/ proguanil	1 daily dose for 3 consecutive days paediatric tablet (62.5 mg atovaquuone + 25 mg proguanil) adult tablet (250 mg atovaquone + 100 mg proguanil) dosage according to body weight
artesunate + doxycycline or clindamycin	2 mg/kg artesunate + 3.5 mg/kg doxycycline once daily for 7 days or 2 mg/kg artesunate once daily for 7 days + 10 mg/kg clindamycin twice daily for 7 days
quinine	8 mg/kg every 8 hours for 7 days
doxycycline	*adults >50 kg:* 800 mg for 7 days (day 1: 2 tablets at 0, 12 hrs, days 2-7: 1 tablet daily) *children >8 years of age* for 7 days dosage according to body weight
clindamycin	*<60 kg:* 5 mg/kg 4 times daily for 7 days *>60 kg:* 300 mg/kg 4 times daily for 7 days
mefloquine	25 mg/kg as split dose (initial dose of 15 mg/kg followed by 10 mg/kg administered after 6-24 hrs)
chloroquine	25 mg base/kg daily divided in 3 doses (10 mg/kg, 10 mg/kg and 5 mg/kg) for 3 consecutive days (do not use in treatment of *P. falciparum* malaria)
primaquine	0.25 mg base/kg once daily for 14 days; 0.5 mg base/kg daily in South-East Asia and Oceania (*P. vivax* and *P. ovale* infection)

Source: WHO. Guidelines for the treatment of malaria. Second edition, 2010 (13)
WHO. International travel and health, 2011 (14)

In treatment of *Plasmodium vivax* malaria one of the following regimens are used:

- chloroquine in combination with primaquine is the treatment of choice if no resistance to chloroquine is observed,
- dihydroartemisinin/piperaquine or artemether/lumefantrine in combination with primaquine is used in treatment of chloroquine-resistant *P. vivax* malaria; in the event of unavailability of the drugs listed, quinine can be used,
- administration of primaquine (which destroys hepatic schizonts thus preventing relapses of the disease) can lead to life-threatening complications, e.g. blood haemolysis, in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals, G6PD deficiency should therefore be excluded prior to initiation of the primaquine treatment.

P. ovale malaria can be treated in the same way as malaria caused by *P. vivax* (chloroquine + primaquine).

P. malariae malaria can be treated in the same way as malaria caused by *P. vivax* although it does not require administration of primaquine.

P. knowlesi malaria (adult forms can be mistaken for *P. malariae* in light microscopy) can be treated in the same way as uncomplicated malaria caused by other *Plasmodium* species.

Treatment of *P. falciparum* malaria is more complex than that of malaria caused by other *Plasmodium* species due to increasing resistance of the parasite to antimalarial medication. Individuals suffering from severe form of *P. falciparum* malaria should be treated at intensive care unit; artesunate being the drug of choice, administered intravenously or intramuscularly. Alternatively, artemeter or quinine can be used if artesunate is not accessible (tab. II). After the initial period of at least 24 hours of parenteral administration of drugs according to the aforementioned regimens, ACT therapy (artesunate + clindamycin or quinine + clindamycin) should follow (15).

Table II. Recommended drugs for the treatment of severe forms of malaria
Tabela II. Środki farmaceutyczne stosowane w leczeniu ciężkich postaci malarii

Drug name	Dosage regimen
artesunate	2.4 mg/kg iv or im at 0, 12 and 24 hrs, then once daily *children:* treatment as above
artemether	3.2 mg/kg im (initial dose); following days: 1.6 mg/kg once daily *children:* treatment as above
quinine	20 mg salt/kg iv infusion or im in 3 split doses every 8 hrs (initial dose), followed by 10 mg salt/kg im in 3 split doses every 8 hrs *children:* treatment as above/in children the same dosing applies caution: iv administration rate should not exceed 5 mg salt/kg/h

Source: WHO. Guidelines for the treatment of malaria. Second edition, 2010 (13)

Stand-by emergency treatment (SBET*).* In cases where fever of an unknown origin occur in tourists travelling to malaria-endemic regions where there is no availability of diagnostic testing, a stand-by emergency treatment should be used according to current indications for the use of particular drugs. SBET is

also advised to contract workers offered short-term overseas employment in malaria-endemic regions (in Switzerland and Great Britain arthemeter/lumefantrine has been registered for stand-by emergency treatment of malaria in travelers) (16).

Treatment of malaria in pregnant women. A combination of quinine and clindamycin administered for 7 days is the treatment of choice in uncomplicated malaria in the first trimester of pregnancy. In the second and third trimesters, the treatment with a combination of clindamycin and quinine/artesunate is recommended for the duration of 7 days. In malignant malaria in the first trimester of pregnancy, a combination of quinine and clidamycin or artesunate and clindamycin is recommended; in the second and third trimesters, artesunate is the drug of choice. Chloroquine is safe in the treatment of *P. vivax* infection providing no resistance to the drug had been observed. Primaquine is not recommended as a prophylactic measure against relapses of *P. vivax* and *P. ovale* malaria in pregnant women. There is insufficient clinical data concerning safe use of other amtimalarial medication (artemether/lumefantrine, atovaquone/proguanil and dihydroartemisinin/piperaquine) in the treatment of malaria in pregnant women (17,18).

Treatment of malaria in young children and infants
Chloroquine is used in treatment of malaria caused by *P. vivax*, *P. ovale* and *P. malariae*, no resistance to the drug has been observed. In severe forms of malaria, artesunate administered intravenously or intramuscularly is the treatment of choice. Alternatively, artemeter or quinine can be used if artesunate is unavailable. After an initial period of parenteral administration of the aforementioned medications over no less than 24 hours, oral therapy with artesunate and clindamycin or quinine and clindamycin should follow.

Stand-by emergency treatment: artemether/lumefantrine (children weighing less than 5 kilograms, limited clinical data), atovaquone/proguanil (children weighing more than 5 kilograms, limited clinical data), dihydroartemisinin/piperaquine (children weighing more than 10 kilograms, limited clinical data) (13,19).

Table III. Type of prevention depending on the risk of malaria
Tabela III. Rodzaj profilaktyki przeciwmalarycznej w zależności od stopnia zagrożenia

Level of risk	Risk of transmission	Type of prevention
Very low risk	limited risk of transmission	repellents, bednets
Low risk	risk of *P. vivax* transmission only; *P. falciparum* susceptible to chloroquine	repellents, bednets, chloroquine
Medium risk	risk of both *P. vivax* and *P. falciparum* transmission; resistance to chloroquine (Nepal, Sri Lanka, Tajikistan, certain regions of Columbia and India)	repellents, bednets, chloroquine + proguanil or atovaquone/proguanil, doxycycline, mefloquine
High risk	(a) high risk of *P. Falciparum* transmission, high antimalarial drug resistance; (b) medium/low risk of *P. Falciparum* transmission, high antimalarial drug resistance; in areas of low risk of *P. falciparum* transmission combined use of repellents and SBET therapy can be considered	repellents, bednets, atovaquone/proguanil, doxycycline, mefloquine (depending on *Plasmodium* resistance)

Source: WHO. International travel and health, 2011 (14)

Table IV. Recommended drugs used in chemoprophylaxis of malaria
Tabela IV. Leki stosowane w chemioprofilaktyce malarii

Drug name	Dosing	Duration of chemoprophylaxis	Comments
atovaquone/proguanil	*11-20 kg:* 62.5mg atovaquone + 25mg proguanil (1 paediatric tablet) daily *21-30 kg:* 2 paediatric tablets daily *31-40 kg:* 3 paediatric tablets daily *>40 kg:* 250mg atovaquone + 100mg proguanil (1 adult tablet) daily	start 1-2 days before departure and continue for 7 days after return	registered for malaria chemoprophylaxis up to a maximum of 4 weeks (in some countries up to 1 year) decrease of drug serum concentration in patients treated with metoclopramide or tetracyclines
doxycycline	*adults:* 100 mg (1 tablet) daily	start 1-2 days before departure and continue for 28 days after return	possible gastrointestinal, gynealogical and/or dermatological adverse reactions
mefloquine	*adults:* 250 mg (1 tablet) weekly	start 1-2 weeks before departure and continue for 4 weeks after return	possible neuropsychiatric adverse reactions; increased serum drug concentration in patients treated with ampicillin, tetracyclines and/or metoclopramide
chloroquine	*adults:* 300 mg (2 tablets) weekly	start 1-2 weeks before departure and continue for 4 weeks after return	contraindications: epilepsy, psoriasis
proguanil	*adults:* 200 mg (2 tablets) daily	start 1-2 days before departure and continue for 28 days after return	use only in combination with chloroquine

Source: WHO. International travel and health, 2011 (14)

ANTIMALARIAL PROPHYLAXIS

The choice of antimalarial prophylaxis depends on the risk of malaria transmission in a particular region. Principal preventive measures include:

- use of appropriate prophylactic malaria drug regimens,
- individual protection from mosquito bites: bednets, repellents (containing 30 to 50% DEET – N,N-diethyl-*meta*-toluamide), adequate protective outfit (long sleeves),
- avoidance of outdoor activities between dusk and dawn,
- use of air-conditioning in rooms and installation of nets on windows and ventilation strips (tab. III).

According to the recommendations by Centers of Disease Control and Prevention and World Health Organization, the following pharmaceuticals should be used in malaria-endemic regions (tab. IV):

Out of the drugs specified atovaquone/proguanil, doxycycline and mefloquine are widely used in chemoprophylaxis of malaria. Because of growing *Plasmodium* resistance, chloroquine is found effective in certain regions of the world only (Central America, North Africa, Middle East), which considerably limits its use.

Antimalarial chemoprophylaxis in pregnant women. Pregnancy should be avoided during antimalarial treatment as well as within: one week after discontinuation of doxycycline, three weeks after discontinuation of atovaquone/proguanil, and three months after discontinuation of mefloquine. There are no contraindications for the use of recommended prophylaxis and chemoprophylaxis of malaria in areas of very low (repellents), low (repellents, chloroquine) and medium (repellents, chloroquine plus proguanil) risk of transmission. In areas of high risk of malaria transmission mefloquine can be used in the second and third trimesters. Doxycycline is contraindicated throughout pregnancy. There is insufficient clinical data concerning safe use of atovaquone/proguanil during pregnancy (20).

Antimalarial chemoprophylaxis in young children and infants. Chloroquine, proguanil and mefloquine are recommended in breastfeeding mothers. Doses should be adjusted according to body weight. Bitter taste of certain antimalarial drugs can be alleviated by their administration with sweet foods. Chloroquine and proguanil are considered safe in young children and infants, although their use is limited due to emerging *Plasmodium* resistance. Mefloquine can be administered to infants weighing more than 5 kilograms. Atovaquone/proguanil is recommended in children weighing more than 11 kilograms (in USA, Canada, Belgium and France in children over 5 kilograms of bodyweight). Doxycycline is contraindicated in children under 8 years of age (13,21).

REFERENCES

1. Murray CJ, Rosenfeld LC, Lim SS, i in. Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 2012;379(9814):413-31.
2. Mali S, Kachur SP, Arguin PM. Malaria surveillance – United States, 2010. MMWR Surveill Summ 2012;61(2):1-17.
3. Stępień M. Malaria w Polsce w 2009 roku. Przegl Epidemiol 2011;65:297-299.
4. Tatem AJ, Huang Z, DAS A, i in. Air travel and vector-borne disease movement. Parasitology 2012;3:1-15.
5. Sabbatani S, Fiorino S, Manfredi R. Plasmodium knowlesi: from Malaysia, a novel health care threat. Infez Med 2012;20(1):5-11.
6. Murphy SC, Prentice JL, Williamson K, i in. Real-time quantitative reverse transcription PCR for monitoring of blood-stage Plasmodium falciparum infections in malaria human challenge trials. Am J Trop Med Hyg 2012;86(3): 383-94.
7. Hoffman SL, Campbell CC, White NJ. Malaria. In: Guerrant RL, Walker DH, Weller PF, ed. Tropical Infectious Diseases. Principles, Pathogens, & Practice. 2nd Ed. Philadelphia: Churchill Livingstone Elsevier; 2006:1024-32.
8. John DT, Petri WA. Medical Parasitology. 9th Ed. St. Louis: Saunders Elsevier; 2006:79-87.
9. White NJ. Malaria. In: Cook GC, Zumla AI, ed. Manson's Tropical Diseases. 22nd Ed. London: Saunders Elsevier; 2009:1201-33.
10. Schwartz E. Malaria in Travelers: Epidemiology, Clinical Aspects, and Treatment. In: Schwartz E, ed. Tropical Diseases in Travelers. Oxford: Wiley-Blackwell; 2009:187-96.
11. Garcia LS. Diagnostic Medical Parasitology. 5th Ed. Washington DC: American Society for Microbiology; 2007:155-161.
12. Lalloo DG, Shingadia D, Pasvol G, i in. UK malaria treatment guidelines. J Infect 2007;54(2):111-21.
13. WHO guidelines for the treatment of malaria. Geneva: World Health Organization 2010.
14. WHO international travel and health. Geneva: World Health Organization 2011.
15. van Vugt M, van Beest A, Sicuri E, i in. Malaria treatment and prophylaxis in endemic and non-endemic countries: evidence on strategies and their cost-effectiveness. Future Microbiol 2011;6(12):1485-1500.
16. Schlagenhauf P, Petersen E. Malaria Chemoprophylaxis: Strategies for Risk Groups. Clin Microbiol Rev 2008;21(3):466-72.
17. Mc Gready R, Lee S, Wiladphaingern J, i in. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis 2012;12(5):388-96.
18. Smith Paintain L, Antwi GD, Jones C, i in. Intermittent screening and treatment versus intermittent preventive treatment of malaria in pregnancy: provider knowledge and acceptability. PLoS One 2011;6(8):e24035.

19. Atwine D, Balikagala B, Bassat Q, i in. A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: a randomized trial. PLoS Med 2011;8(11):e1001119.
20. Irvine MH, Einarson A, Bozzo P. Prophylactic use of antimalarials during pregnancy. Can Fam Physician 2011;57(11):1279-81.
21. Venturini E, Chiappini E, Mannelli F, i in. Malaria prophylaxis in African and Asiatic children traveling to their parents' home country: a Florentine Study. J Travel Med 2011;18(3):161-4.

Received: 10.05.2012 r.
Accepted for publication: 25.09.2012

Address for correspondence:
Krzysztof Korzeniewski
Wojskowy Instytut Medyczny
Zakład Epidemiologii i Medycyny Tropikalnej
ul. Grudzińskiego 4
81-103 Gdynia
tel. +48 665 707 396
e-mail: kktropmed@wp.pl