REVIEW ARTICLES

Special Infectious Disease Risks of Expatriates and Long-Term Travelers in Tropical Countries. Part I: Malaria

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Malaria risk is dependent upon the entomological inoculation rate actually faced by the long-term traveler. Risk is cumulative, increases with duration of exposure, is greatest in rural and periurban areas, and least in urban centers. Risk may be zero in some urban centers, especially during dry seasons. Chemoprophylaxis compliance is hindered by the high adverse event rate often reported by users, is often suboptimal in expatriates, and decreases with duration of stay. Compliance with personal protection measures may also be suboptimal, and use of insecticide-treated nets and effective repellents should be encouraged. Alternative strategies to mitigate risk include seasonal chemoprophylaxis, nonuse of chemoprophylaxis with rapid treatment, self-testing, self-treatment where competent care and quality drugs are unavailable, and vector control. Choice of strategies will depend upon assessment of actual risk and likely compliance, with a combination of measures usually appropriate.

Long-term travelers face a number of health risks, which vary with posting, itinerary, and circumstances. "Long term" is considered travel >4 weeks, although the UK definition is "those visiting or traveling through malaria-endemic countries for >6 months."[1] The category includes, among others, backpackers and expatriates resident in a region. Military and humanitarian field operations will not be considered by this article. Long-term travelers' risks, and their management, differ frequently from those of short-term travelers, as reference to malaria illustrates.

Malaria

Estimating the Risk

Falciparum malaria is potentially fatal in nonimmunes and will be the greatest risk facing many long-term travelers. Exact risk will vary with location, occupation, lifestyle, and activities. Nocturnal activity increases potential risk. The risk of serious adverse events from chemoprophylaxis may exceed that of malaria at some malarious destinations.[2]

Urban residence in Africa may reduce malaria risk, while in Asia, official statistics may underestimate urban malaria risk.[3]

A meta-analysis by Robert and colleagues[4] found a gradient of malaria risk in Africa: expressed as the entomological inoculation rate (EIR), risk increased from urban centers (mean = 7.1 bites/person/year; range 0–30), through periurban (mean = 45.8) to rural areas (mean = 167.7). Comparisons showed high levels of statistically significant differences in EIRs between all three residential options ($p < 0.001$, Mann Whitney), with the exception of the periurban–rural difference ($p = 0.051$). The actual risk of clinical malaria depends upon the EIR and "infection efficiency," a measure of the ability of infected bites to initiate clinical disease. Infection efficiency is rarely 100%, reducing further the risk of clinical malaria.

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Coene[5] also found an urban–rural gradient in Kinshasa, which had a mean urban EIR of 29.2 and a mean rural EIR of 453. *Anopheles* vectors in rural areas were found to live longer and more likely to be infected with *Plasmodium falciparum*. Importantly, Coene found that urban transmission virtually ceased in the later stages of the dry season, that is, the actual EIR approached or reached 0. Evidence confirms that EIR is influenced by climate in Africa: mean EIR is 0.96 in dry savannah and Sahel urban centers, rising to 12.62 in wet savanna and forest zone urban centers.[4,6] Amexo and colleagues[6] quote a malaria overdiagnosis rate of 96% in the Sahel during the dry season, indicating virtual malaria absence.

Transmission within urban and rural areas may vary enormously, along with local *Anopheles* density, species, and microenvironment: Trape and Zoulani[7] found a mean EIR of 22.5 in Brazzaville, but rates varied by district from <0.33 (equivalent to less than 1 infected bite every 3 years) to >100. Karch and colleagues[8] found a similar urban–rural gradient in the Democratic Republic of Congo, with just 1 infective bite every 128 nights in urban Kinshasa but 1.7 infective bites every night in semirural areas.

A study of Kenyan children aged <6 years, whose immune status parallels that of nonimmune expatriates, showed a high degree of correlation between the actual EIR for each child, the child's likelihood of developing parasitemia, and the consequent parasitemia density. Cumulative infective bite exposure and exposure duration were significant predictors of parasitemia density.[9] Eono and colleagues[10] found that length of stay correlated with the likelihood of suffering clinical malaria and that risk was cumulative. Nevertheless, not all expatriates develop clinical malaria. The use of EIR as a predictor of risk to expatriates has been suggested by Rombo, who points out that local incidence rates, which exclude asymptomatic infections, are of little relevance to nonimmunes, such as expatriates.[11]

It can be seen that the long-term traveler will benefit from a well-informed and scientifically sound risk assessment.

Chemoprophylaxis

Real and Perceived Adverse Events

Chemoprophylaxis, supported by personal protection measures, is the mainstay of malaria prevention in short-term travelers, but blanket application of this strategy to expatriates is problematic.

Adverse events, real or perceived, discourage compliance with chemoprophylaxis. Schlagenhauf and colleagues[12] studied traveler-reported adverse event rates in short-term travelers. The first phase of this study compared adverse event rates during predeparture use of mefloquine, doxycycline, atovaquone/proguanil, chloroquine with proguanil, and placebo: 16% of subjects complained of adverse events while taking placebo, 15% while taking atovaquone/proguanil, 16% while taking doxycycline, 22% while taking mefloquine, and 24% while taking chloroquine and proguanil ($p = 0.19$, χ^2). Although the results show that chemoprophylaxis was as well tolerated as placebo, travelers nevertheless complained of adverse events. A poll of subjects on return revealed 85% as believing they had suffered at least one adverse event during chemoprophylaxis use. This rate seems very high and at odds with clinical experience. Chemoprophylaxis likely received the blame for symptoms attributable to other causes. Schlagenhauf's reported rates indicate just how poorly travelers perceive and tolerate chemoprophylaxis.

Overbosch[13] found that gastrointestinal symptoms attributed by users to chemoprophylaxis occurred with almost identical frequency regardless of chemoprophylactic regimen. When adverse events were probed and attributed to either drug or travel, exactly the same pattern and frequency of symptoms was found. Overbosch estimated that 32% of tropical travelers would experience diarrhea; presumably, many on malaria prophylaxis would attribute diarrhea to their medication. These findings may correlate with Schlagenhauf's and show that chemoprophylaxis has an undeservedly bad reputation.

A separate issue is the neuropsychiatric adverse effects attributed to mefloquine. Overbosch deduced, using the methodology described above, that tropical travel itself causes 8% of chemoprophylaxis users to complain of neuropsychiatric symptoms. There is however much and weighty evidence from other studies to support mefloquine being disproportionately associated with dramatic and disabling neuropsychiatric adverse events.

Meier searched the UK General Practice Research Database, finding over 16,000 mefloquine users.[14] Looking only for adverse events serious enough to warrant medical attention, he found increased odds among current mefloquine users for panic attacks [odds ratio (OR) 2.7, 95% confidence interval (CI): 1.1–6.5; $p < 0.05$) and psychosis (OR 8.0, 95% CI: 1.0–62.7; $p < 0.05$).

Meier did not look for neuropsychiatric adverse events that were not sufficiently serious to warrant

medical attention. Van Riemsdijk and colleagues[15] looked for all mood changes and found increased rates of mood deterioration in female and first-time users of mefloquine. These decreases were found prior to departure, discounting Overbosch's travel effect. In a separate case-control study that counted the number of consultations for psychiatric symptoms while abroad, van Riemsdijk found that mefloquine use increased the odds of developing psychiatric symptoms by 3.5 (95% CI: 1.4–8.7). The odds increase was even greater in female users, with a striking OR of 47.1 (95% CI: 3.8–578.6). In subjects with a history of mental illness, the odds rose to 8 (95% CI: 1.8–35.8).[16]

Barrett and colleagues'[17] retrospective postal survey of mefloquine users found 0.7% suffered neuropsychiatric adverse events that disrupted daily activities and 0.002% required hospitalization. Alcohol plays a large part in the social life of many expatriates, and anecdotal evidence supports the view that this may exacerbate mefloquine's neurotoxicity.[18–20]

Given the poor perceptions of chemoprophylaxis demonstrated in the Schlagenhauf study, and the real problems associated with mefloquine, the actual and perceived risk–benefit ratios of chemoprophylaxis may dissuade many expatriates from long-term use. Given too the stresses that may accompany settling into a new country and job, and the readiness to attribute symptoms to chemoprophylaxis, it is easy to imagine expatriates and long-term travelers abandoning chemoprophylaxis as they suffer travel- and stress-related symptoms.

Concerns over the consequences of long-term chemoprophylaxis are often aired by expatriates. Although there is a paucity of data supporting long-term chemoprophylaxis with doxycycline, the drug is in regular use for extended durations for other indications.[21] Currently available data for mefloquine do not show additional risk with long-term use, while chloroquine use at 300 mg/week for >5 years demands biannual ophthalmic assessment. Both constituents of atovaquone/proguanil have been used for prolonged periods, and there is no labeling restriction on long-term use in the United States, although there is in Europe.

Compliance

Actual studies of expatriate chemoprophylaxis use and compliance are few and have been conducted mainly in Africa. They generally show disappointing results in terms of both compliance and appropriateness of drug used. Eono and colleagues[10] found compliance rates of 40.5% in Abidjan, with 17.5% of subjects using dangerous or inappropriate chemoprophylaxis, for example, amodiaquine. Carme[22] tracked compliance in Brazzaville and found a steady decline within the same community over a 3-year period; length of stay correlated inversely with chemoprophylaxis usage. Carme and others describe a tendency for expatriates to abandon chemoprophylaxis with increasing length of stay.[1,22,23] The official French view is that compliance by long-term travelers may be "unrealistic."[24]

Lobel and Gerber[25] report implied compliance rates of 90% to 95% in Peace Corps Volunteers, but this closely monitored and supervised group is unlikely to be representative of most expatriates. Harries and colleagues[26] reported a remarkably high level of chemoprophylaxis use in a survey of British expatriates in Malawi in 1988: 96% of respondents (N = 293, 89% response rate) reported regular chemoprophylaxis use. This equates to compliance for the whole community being in the range 85% to 96%. However, completed questionnaires appeared not to be anonymous in what was a small community. Harries did find appropriateness of regimen to be a problem though, with 48% of those taking proguanil (accepted in solo use at the time of the study) doing so at an inappropriate dose. A recent questionnaire-based study in of expatriates in Mali revealed that 31% of subjects claiming compliance with an effective chemoprophylaxis regimen developed malaria, most likely indicating very poor compliance.[27] Responses to questionnaires may overstate compliance, as demonstrated by Landry and colleagues' study of short-term travelers prescribed mefloquine. Forty-eight percent of subjects claimed compliance in questionnaire responses; yet, microchipped medicine containers revealed that only 29% had actually been compliant.[28] It is unlikely that the high compliance rates reported by Lobel and Harries would be found in the average expatriate community, and truly high compliance rates are probably achieved only in directly supervised military settings.

Expatriates may express concerns over the safety of long-term chemoprophylaxis,[29] especially as they may be resident in endemic areas for 10 or even 20 years, and there are no convincing studies on the safety of very long-term chemoprophylaxis that travel health advisors can point to when trying to reassure travelers and boost compliance.

Compliance by expatriates to personal prevention measures may also be suboptimal. Eono and colleagues[10] found a bed net usage rate of only 7.5% among expatriates in Ghana, and Jute and Toovey[27] 13% in Mali. Examination of Harries 1988 survey

of Britons resident in Malawi reveals that compliance with personal protection measures decreases as they became more intrusive or require greater daily effort: 92% of respondents had screened rooms, 62% burnt coils, 45% used insecticidal sprays, and only 28% used bed nets.[26] There is evidence supporting the claim that air-conditioning reduces the risk of malaria infection.[30] This may be an "effortless" form of personal protection measure that should be considered for expatriates.

The belief among some expatriates that use of chemoprophylaxis prevents development of immunity may affect compliance: some expatriates believe that long-term residence in malarious areas imparts immunity. Expatriates should be disabused of the belief that they may develop immunity to malaria and assured that chemoprophylaxis does not modulate their immune responses.

Chemoprophylaxis or Not?

Knobloch[23] argues, and consensus agrees, that malaria chemoprophylaxis should be individualized. This argument applies both to drug choice and the decision as to whether long-term chemoprophylaxis should be recommended.

Adera and colleagues report a malaria outbreak among expatriates in Uganda in 1992, during which incidence was almost seven times that of the preceding 6 years combined. During this outbreak, expatriates not taking chemoprophylaxis were 10 times more likely to develop clinical malaria than individuals compliant with a standard regimen (Relative Risk 10, 95% CI: 2.7–37.0).[31] Risk varied within the expatriate community, however, being greatest for African Americans and those <20 years old. Clearly, as the observed risk varied with age, race, and year, the chemoprophylaxis risk–benefit ratio was not the same for all expatriates. Although Adera concludes, quite rightly, that compliance with chemoprophylaxis is important in preventing disease, it is a moot question whether those with the lowest risk would have benefited from chemoprophylaxis every year, all year.

Expatriates often choose to follow the advice of locals and other expatriates on malaria prevention, rather than that of experts in their home countries. The reasons for this are unclear, but the phenomenon is well known among travel medicine practitioners.[23,32,33] The use of long-term prophylaxis may require repeated contact with health care providers for repeat prescriptions. Additionally, it is not uncommon practice for individuals on long-term chemoprophylaxis to undergo regular screening for the liver function abnormalities associated with mefloquine.[30,34] These factors add to the cost and inconvenience of long-term chemoprophylaxis.

While long-term chemoprophylaxis may be the ideal, it is clear that desired compliance levels will rarely be attained. Compliance with intrusive personal protection measures may also be unsatisfactory. Given such poor compliance, alternative strategies tailored to the individual's risk and behavior profile are needed. These may include seasonal use of chemoprophylaxis, short-term use of chemoprophylaxis for field trips, emergency stand by medication, ensuring ready access to competent medical care, and vector control methods.

Seasonal Chemoprophylaxis

Seasonality of malaria in some locations may permit chemoprophylaxis use confined to the wet and early dry season. Expatriates adopting this strategy should ideally do so under expert guidance and after proper quantification of the local risk. They will need to remain on guard for malaria symptoms during the dry season. Clinicians may find MARA Collaboration risk maps useful when considering this strategy (www.mara.org.za).

Access to Competent Medical Care

Early presentation with prompt and effective treatment of malaria may be lifesaving. Accordingly, expatriates must be educated on malaria symptoms and the importance of early presentation, assuming adequate treatment is available. The misperception that malaria may present without fever should be dispelled, although the possibility of modified and afebrile presentations under prophylaxis should be remembered.

Unfortunately, access to competent medical care may be difficult in many developing countries, especially in remoter locations. It seems unfortunately true that competence in dealing with malaria is inadequate in many malarious environments, where there may be a tendency to overdiagnose malaria.[6] This may explain pseudoresistance, the alleged clinical failure of effective drugs. Reasons for these inadequacies are many but include a lack of physical resources and skilled personnel. Treatment regimens in developing countries may also not be appropriate for nonimmune individuals.[35] Ideally, sources of competent care should be identified before posting as the local and expatriate populations cannot always be relied upon to make sound recommendations.

Where competent care cannot be identified prior to posting, the expatriate is better advised to take chemoprophylaxis. It is to be hoped that, if

and when the expatriate "lapses" from chemoprophylaxis, he/she will have identified a source of competent care and understand more fully the local malaria risk.

Emergency Stand by Medication

Many expatriates purchase antimalarials locally in-country, which may be problematic, as the sale of antimalarials is effectively unregulated in parts of Africa and Southeast Asia, where much of the antimalarial drug supply is counterfeit. Dondorp and colleagues[36] found 53% of the artesunate sampled in Southeast Asia to be fake, with a significant percentage of mefloquine containing subtherapeutic doses. Similar findings are reported from Africa, where drugs supplied through recognized pharmacies may be substandard or counterfeit. Taylor and colleagues[37] found 48% of antimalarials sampled in Lagos and Abuja to be substandard, with some samples containing no active ingredient.

Given the possible difficulties in accessing competent medical care and quality medication, it may be necessary to provide the expatriate with the means to treat him/herself or his/her family. Known as "emergency stand by medication," this strategy requires the provision of an effective but easily used and well tolerated drug, assessment of the expatriate's ability to use the drug sensibly, and education on malaria symptoms.[32] It should be emphasized that self-treatment is not an alternative to competent medical care but a stopgap measure to be used until competent care is available. Clinicians may need to accept expatriates erring on the side of caution and overdiagnosing malaria.

Debate continues on the role of self-testing with rapid antigen kits, although it is recognized that there may be place for their use in "long-term stay."[38] If expatriates are provided with test kits, comprehensive instruction and demonstration should be given, and the traveler should demonstrate his ability to use the test. The expatriate should be clearly warned that false-negative and false-positive results occur and that treatment may need to be taken despite negative tests. Additionally, rapid antigen tests remain positive for days and sometimes weeks after curative treatment, which may be confusing to the lay user.[39,40] The expatriate should be informed that self-testing is not a substitute for skilled microscopy.

The UK, French, Dutch, Belgian, German, Swiss, Canadian, and US guidelines all consider the use of emergency standby medication acceptable when no other alternative is available but all state it is not a substitute for competent medical care.[24,33,41–45] Emergency stand by medication may be a useful strategy to adopt when counseling long-term travelers.[29,32]

While thoughtful medical opinion sees emergency stand by medication as a stopgap until competent medical care is reached,[32] it must be recognized that this may simply not be possible in many expatriate situations. In such situations, and where evacuation is not feasible, emergency stand by medication assumes even greater importance.

Emergency stand by medication may also act as an alternative strategy for the expatriate who declines or lapses from chemoprophylaxis. This approach has increasingly been taken by Japanese expatriates resident in African city centers[46] and observed among Belgian expatriates resident in Central Africa's Lubumbashi and Kinshasa for many years—many of them for decades (van Gompel, unpublished data).

Personal Protection Measures

The use of insecticide-treated bed nets and effective mosquito repellents should be encouraged to provide protection against malaria and other nocturnal arthropod-borne infections; air-conditioning of sleeping quarters is recommended and may supplant the requirement for nets, but the air must be correctly filtered with a mosquito screen at the inlet. These measures assume greater importance when chemoprophylaxis is stopped by expatriates. Exposure risks faced by the long-term itinerant will vary depending on the environments in which they travel, and compliance with personal insect protection measures will be problematic at times: abandonment of appropriate chemoprophylaxis by this group is usually best discouraged.

Vector Control

This includes the application of residual insecticides, larviciding, attention to drainage, accommodation screening, establishment of accommodation away from likely breeding sites, provision of air-conditioning, and site hygiene. Large employers in tropical environments often attend to many of these activities. In instances where they do not, the expatriate should be advised on the practical application of available vector control methods. Residual spraying and larviciding are best conducted by experts.

Vector control programs should ideally follow a baseline entomological assessment that establishes vector species and habits. This enables rational, environmentally acceptable, and cost-effective control, which is best conducted by those with expertise in this field.

Women and Children

Malaria in pregnancy is associated with increased morbidity, and risk of maternal and fetal mortality. Advice on the teratogenic potential of chemoprophylaxis and the timing of conception may need to be given.[47,48] Overall, pregnancy is best avoided by nonimmunes in malarious areas.

Expatriates planning to travel with young families should be advised that children ≤5 years of age may be at increased risk of complicated disease should they contract malaria. There is evidence that insufficient attention is paid by some expatriates to malaria prevention in their children.[49] The selection of appropriate personal protection measures and chemoprophylaxis for children must, as with adults, be individualized, and pay close attention to age, weight, and health status.[50]

Conclusions

Malaria is likely to be the expatriates' greatest infectious disease threat. Mitigation may require different approaches to those adopted for short-term travelers. Sound management of the risk requires an understanding of the EIR the expatriate will face at his/her posting, and the variable risk the long-term traveler may experience along his/her itinerary. Such information is unfortunately often unavailable. In situations where the risk may not justify continuous chemoprophylaxis, or the frequent situation where compliance may be suboptimal, additional and alternative strategies will need careful contemplation, despite their unpalatability to the clinician. The seasonal use of chemoprophylaxis, nonuse of chemoprophylaxis with rapid treatment, self-testing, self-treatment with emergency stand by medication, and vector control may all be considered.

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References

1. Hughes C, Tucker R, Bannister B, Bradley DJ. Malaria prophylaxis for long-term travelers. Commun Dis Public Health 2003; 6:200–208.
2. Steffen R, DuPont HL, Wilder-Smith A. Basics of malaria prophylaxis. Manual of travel medicine and health. 2nd Ed. Hamilton, ON: BC Decker Inc, 2003:77–85.
3. Yadav RS, Bhatt RM, Kholi VK, Sharma VP. The burden of malaria in Ahmedabad city, India: a retrospective analysis of reported cases and deaths. Ann Trop Med Parasitol 2003; 97:793–802.
4. Robert V, MacIntyre K, Keating J, Trape JF. Malaria transmission in urban sub-Saharan Africa. Am J Trop Med Hyg 2003; 68:169–176.
5. Coene J. Malaria in urban and rural Kinshasa: the entomological input. Med Vet Entomol 1993; 7: 127–137.
6. Amexo M, Tolhurst R, Barnish G, Bates I. Malaria misdiagnosis: effects on the poor and vulnerable. Lancet 2004; 364:1896–1898.
7. Trape JF, Zoulani A. Malaria and urbanization in central Africa: the example of Brazzaville. Part II: results of entomological surveys and epidemiological analysis. Trans R Soc Trop Med Hyg 1987; 81 (Suppl 2):10–18.
8. Karch S, Asidi N, Manzambi ZM, Salaun JJ. [The Anopheles fauna and the transmission of human malaria in Kinshasa (Zaire)]. Bull Soc Pathol Exot 1992; 85:304–309.
9. McElroy PD, Beier JC, Oster CN, et al. Dose- and time-dependent relations between infective Anopheles inoculation and outcomes of Plasmodium falciparum parasitemia among children in western Kenya. Am J Epidemiol 1997; 145:945–956.
10. Eono P, Polaert C, Louis JP. [Malaria in expatriates in Abidjan]. Med Trop (Mars) 1999; 59:358–364.
11. Rombo L. Who needs drug prophylaxis against malaria? My personal view. J Travel Med 2005; 12:217–221.
12. Schlagenhauf P, Tschopp A, Johnson R, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ 2003; 327:1078.
13. Overbosch D. Post-marketing surveillance: adverse events during long-term use of atovaquone/proguanil for travelers to malaria-endemic countries. J Travel Med 2003; 10 (Suppl 1):S16–S20.
14. Meier CR, Wilcock K, Jick SS. The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. Drug Saf 2004; 27:203–213.

15. Van Riemsdijk MM, Ditters JM, Sturkenboom MC, et al. Neuropsychiatric events during prophylactic use of mefloquine before travelling. Eur J Clin Pharmacol 2002; 58:441–445.
16. van Riemsdijk MM, Sturkenboom MC, Pepplinkhuizen L, Stricker BH. Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in the Netherlands. J Clin Psychiatry 2005; 66:199–204.
17. Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. BMJ 1996; 313: 525–528.
18. Lebain P, Juliard C, Davy JP, Dollfus S. [Neuropsychiatric symptoms in preventive antimalarial treatment with mefloquine: apropos of 2 cases]. Encephale 2000; 26:67–70.
19. Wittes RC, Saginur R. Adverse reaction to mefloquine associated with ethanol ingestion. CMAJ 1995; 152:515–517.
20. Phillips MA, Kass RB. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. J Travel Med 1996; 3:40–45.
21. Baxter BT, Pearce WH, Waltke EA, et al. Prolonged administration of doxycycline in patients with small asymptomatic abdominal aortic aneurysms: report of a prospective (Phase II) multicenter study. J Vasc Surg 2002; 36:1–12.
22. Carme B. Antimalarial measures in expatriates in the Congo. Trends 1989-1992. Ann Soc Belg Med Trop 1993; 73:91–99.
23. Knobloch J. Long-term malaria prophylaxis for travelers. J Travel Med 2004; 11:374–378.
24. Santé des voyageurs et recommendations sanitaires 2005. Bulletin Épidemiologique Hebdomadaire 2005; (24–25):117–129.
25. Lobel HO, Gerber AR. Long term travelers. In: Schlagenhauf P, ed. Travelers' malaria. Hamilton, ON: BC Decker, 2001:261–269.
26. Harries AD, Forshaw CJ, Friend HM. Malaria prophylaxis amongst British residents of Lilongwe and Kasungu districts, Malawi. Trans R Soc Trop Med Hyg 1988; 82:690–692.
27. Jute S, Toovey S. Knowledge, attitudes and practices of expatriates towards malaria chemoprophylaxis and personal protection measures on a mine in Mali. Travel Med Inf Dis 2006. Available at: www.sciencedirect.com. (Accessed 2006 Jun 13)
28. Landry P, Iorillo D, Darioli R, et al. Do travelers really take their mefloquine malaria chemoprophylaxis? Estimation of adherence by an electronic pillbox. J Travel Med 2006; 13:8–14.
29. Chen LH. Malaria in long term travelers. Travel Medicine Advisor 2006; 7–9.
30. Croft A. Extracts from "Clinical Evidence". Malaria: prevention in travellers. BMJ 2000; 321:154–160.
31. Adera T, Wolfe MS, Guire-Rugh K, et al. Risk factors for malaria among expatriates living in Kampala, Uganda: the need for adherence to chemoprophylactic regimens. Am J Trop Med Hyg 1995; 52:207–212.
32. Bannister B, Hatz C, Toovey S, et al. The role of standby emergency medication for falciparum malaria: current opinion. Travel Med Inf Dis 2004; 2:119–126.
33. Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. Commun Dis Public Health 2003; 6:180–199.
34. Fontanet AL, Houze S, Keundjian A, et al. Efficacy of antimalarial chemoprophylaxis among French residents travelling to Africa. Trans R Soc Trop Med Hyg 2005; 99:91–100.
35. Baird JK, Basri H, Jones TR, et al. Resistance to antimalarials by Plasmodium falciparum in Arso PIR, Irian Jaya, Indonesia. Am J Trop Med Hyg 1991; 44:640–644.
36. Dondorp AM, Newton PN, Mayxay M, et al. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. Trop Med Int Health 2004; 9:1241–1246.
37. Taylor RB, Shakoor O, Behrens RH, et al. Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. Lancet 2001; 357:1933–1936.
38. Jelinek T. Malaria self-testing by travellers: opportunities and limitations. Travel Med Inf Dis 2004; 2:143–148.
39. Biswas S, Tomar D, Rao DN. Investigation of the kinetics of histidine-rich protein 2 and of the antibody responses to this antigen, in a group of malaria patients from India. Ann Trop Med Parasitol 2005; 99:553–562.
40. Iqbal J, Siddique A, Jameel M, Hira PR. Persistent histidine-rich protein 2, parasite lactate dehydrogenase, and panmalarial antigen reactivity after clearance of Plasmodium falciparum monoinfection. J Clin Microbiol 2004; 42:4237–4241.
41. Centers for Disease Control. Prescription drugs for Malaria. Available at: www.cdc.gov/travel/malaria drugs2.htm. (Accessed 2005 Jun 21)
42. Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit (DTG). Empfehlungen zur Malariavorbeugung. Available at: http://www.dtg.mwn.de/pdf/Malaria-DTG-2004-24Sfinal.pdf. (Accessed 2005 Jun 21)
43. Landelijk Coördinatie Centrum Reizigersadvisering. Malaria Prophylaxe Bulletin in Landelijke Protocollen Reizigersadvisering. Landelijk Coördinatie Centrum Reizigersadvisering. Available at: www.lcr.nl. (Accessed 2006 Apr 6)
44. Prins Leopold Instituut voor Tropische Geneeskunde. What to do during a possible malaria attack. Available at: http://www.itg.be/itg/Uploads/MedServ/enoodmal.pdf. (Accessed 2005 Jun 21)
45. Swiss Tropical Institute. Medizinischer Ratgeber. Available at: http://www.safetravel.ch/safetravel/servlet/ch.ofac.wv.wv104j.pages.Wv104Recherche

SimpleCtrl?action=showTheme&ref_theme=5. (Accessed 2005 Jun 21)
46. Reduction of the use of chemoprophylaxis for malaria among Japanese expatriates in tropical Africa. 8th Conference of the International Society of Travel Medicine; May 7, 2003.
47. McGready R, Ashley EA, Nosten F. Malaria and the pregnant traveller. Travel Med Inf Dis 2004; 2:127–142.
48. Carroll ID, Van Gompel A. The pregnant wilderness traveler. Travel Med Inf Dis 2005; 3:225–238.
49. Getting a better understanding of the practice of malaria prevention in children of long-term expatriates in malaria endemic areas. 8th Conference of the International Society of Travel Medicine; May 7, 2003.
50. Fischer PR, Bialek R. Prevention of malaria in children. Clin Infect Dis 2002; 34:493–498.