Continuing Medical Education

FEVER AFTER A STAY IN THE TROPICS

Part 2 : common imported tropical diseases

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INTRODUCTION

There are many tropical diseases which could cause febrile illnesses in travellers. Also cosmopolitan infections represent an important proportion of etiologies, as reminded in the part 1 of this review. It is beyond the scope of this article to discuss all the possible causes of fever in travellers. We will focus on the 5 leading tropical diseases which, together with bacillary dysentery, account for > 50 % of all the causes of fever (see table 1, in part 1). The purpose of this paper is to bring to the readers' attention some recent diagnostic or therapeutic developments, which could be relevant in their daily clinical practice.

MALARIA

Malaria is the result of an infection by any of the 4 species of *Plasmodium (falciparum, vivax, ovale, malariae),* transmitted by night-biting *Anopheles* mosquitoes. Malaria remains one of the most important infectious diseases in the world, affecting 300-500 million persons every year, and causing 1-2 million annual deaths, mostly due to *P. falciparum* infections. Prevalence of imported malaria is increasing everywhere in industrialised countries, reaching in 1999 more than 1500 cases in the USA (1), and more than 13000 cases in Europe (2). The same rising trend has been observed in our centre during the last decade (3). Recently, several European tropical institutes, including the Institute of Tropical Medicine, Antwerp, have created an European network (TropNetEurop) to register imported malaria cases for epidemiological surveillance and alert awareness (4). For example, the network identified an outbreak of malaria in 2000 in travellers returning from Dominican Republic, considered until now as a region with a very low risk of acquiring malaria. These travellers were infected during a transitory epidemic provoked by seasonal labourers coming from Haiti (5).

The risk of contracting malaria during a travel without chemoprophylaxis has been estimated per area (6). The attack rate ranges from > 3/100 persons per months of travel (pmt) in Papua New Guinea and some regions of Africa to 5/10000 pmt in Latin America (excluded the Amazon basin). A thorough travel history is always required, because infection may have even been acquired during a short stop-over (7). Numerous studies have proven that compliance with recommended chemoprophylaxis dramatically reduces the risk and the severity of malaria attacks (8,9). However, for multiple reasons, the knowledge of and compliance with prophylactic regimens are usually low (10,11).

In its early stages, malaria resembles unspecified viral illnesses and is easily overlooked. A high index of

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suspicion is required to make this diagnosis. In our highly "mobile" era, a history of recent travel should be systematically asked for in any patient with febrile illness. Many studies have stressed the absence of specific signs, symptoms or laboratory abnormalities to allow the diagnosis of imported malaria (12-15). In a case-control study matching febrile travellers with and without malaria (14), splenomegaly and thrombocytopenia, although suggestive for malaria when present (specificity > 90%), had only sensitivities of 20 % and 50 % respectively. A tertian fever pattern (peaks of fever every other day), was highly specific (95%) for P. vivax/ovale infections, but had only an overall sensitivity of 40 %. In addition clinicians have also to deal with the widely varying incubation periods of malaria. Almost 90 % of non-immune patients infected with P. falciparum present with fever within 6 weeks after return (15). However, in semi-immune patients, or non-immune travellers who have taken chemoprophylaxis, symptoms may develop later, after a few months and exceptionally after more than 1 year (16). In contrast, only 25 % of infections with the other plasmodia become symptomatic within 6 weeks after return, while one third of the patients develop symptoms after 6 months (15).

While evaluating a patient with suspected or confirmed malaria, one should also judge the severity of the disease, especially in case of *P. falciparum* infection. The World Health Organisation (WHO) has published a list of clinical and biological criteria to recognise complicated malaria (see table) and recommendations to manage this complex issue (17). A complicated course according to the WHO criteria is reported in 4-10 % of the P. *falciparum infections* (12,18,13). Overall mortality related to imported malaria varies between 0 and 5 % (4,18,19). The fatality rate may rise up to 20% in case of complicated malaria, even with the most ad-

Table : Criteria of severe and complicated malaria (WHO 2000)*

- Symptoms of cerebral dysfunction (impaired consciousness, coma, convulsions,...)
- Severe anaemia (Hb < 7 g/dl or hematocrit < 20 %)
- Shock; "algid malaria" (systolic BP < 80 mmHg)
- Adult Respiratory Distress Syndrome (ARDS)
- Jaundice (total bilirubin > 3 mg/dl)
- Haemorrhagic manifestations (or disseminated intravascular coagulation, or thrombopenia < 20000/microl.)
- Acute renal failure (oliguria < 400 ml/24 hrs or creatinin > 3 mg/dl)
- Hypoglycaemia (blood glucose < 40 mg/dl)
- Metabolic acidosis (pH < 7,35 or bicarbonate < 15 mmol/L)
- Hyperlactatemia (raised venous lactate > 5 mmol/L)
- Hyperparasitemia (> 4 % RBC parasitized or > 200000 parasites/microl. in non-immune subjects), or peripheral schizontemia
- Hemoglobinuria (Blackwater fever)

These criteria have been identified as prognostic factors in endemic countries, for non-immune children and semi-immune adults. They should be viewed cautiously in case of non-immune travellers

vanced care. Risk of death has been associated with absence of chemoprophylaxis, delay in diagnosis (patient's or doctor's delay), and patient's age (20,13).

The search for parasites in stained blood films remains the cornerstone of diagnosis. The thick blood film achieves a detection threshold of 50 parasites/µl of blood by an experienced microscopist, corresponding to 0,001 % of red blood cells (RBC) infected. Sensitivity however is lower (average: 0,01 % RBC infected, 500 parasites/µl) in most routine diagnostic laboratories (21). The thin blood film may miss low parasitemia, but provides a greater specificity, an easier identification of plasmodium species, and a more accurate quantification of the parasitemia. Because parasitemia may be undetectable at the onset of symptoms, blood smears should be repeated twice over the next 24 hours, before malaria is excluded. Although the microscopic examination of blood film remains the diagnostic "gold standard", this method is time-consuming, labor-intensive, and requires considerable expertise, particularly at low levels of parasitemia. For these reasons, development of rapid diagnostic tests (RDT) has been promoted by the WHO. The ideal RDT for malaria should be adapted to routine field conditions, which means being rapid, sensitive and cost-effective. The most recent developments on this issue have been reviewed by Moody (22). Several RDT using immunochromatographic dipstick assays are now commercially available. Most of them target the histidine rich protein 2 (HRP-2), produced by asexual stages and young gametocytes of *P. falciparum/ vivax,* and expressed on the infected RBC membrane surface (ParaSight-F (Becton Dickinson, USA), ICT *Pf or Pf/Pv* (Amrad ICT, Australia), PATH Falciparum Malaria IC test (PATH, USA)). Others detect a specific *P. falciparum/vivax* LDH (p-LDH), an enzyme expressed at high levels in asexual stages of malaria parasites (OptiMAL (Flow Inc., USA)). Sensitivity of HRP-2 based tests was shown to be 97-98 % for P falciparum infected febrile travellers, with a parasitemia of > 100 / µl, but only 47%-53 % at lower parasitemia (23,24). Performances of p-LDH based tests are similar for imported malaria. However, they allow also the diagnosis of P. vivax infections, and the monitoring of the response to antimalarial therapy (levels of p-LDH are correlated to the presence of viable parasites) (25,26). As low parasitemia and infections with species other than *P. falciparum* may cause considerable morbidity in non-immune patients, the overall sensitivity of the available RDT must be viewed as only 70 % for detecting imported malaria. These antigenic tests have therefore no additional value in laboratories with sufficient malaria expertise. However, in other settings (emergency) they can be used as a rapid screening test. If positive, conventional microscopy is needed to determine the parasitemia (evaluation of the severity). If negative, and in case of a high level of suspicion, a blood smear is also required (but with a possible delay) to detect low parasitemia or an infection by another species of *Plasmodium* (24). When the plasmodium species cannot be identified at the blood smear examination, RDT may be helpful to identify *P. falciparum* infection. However, the available RDT remain suboptimal for detecting P. vivax, and there is no RDT capable of diagnosing *P. ovale or P. malariae* infections.

The standard treatment for "non falciparum" infections is still based on chloroquine (1500 mg distributed in a 3-day-course). In non-pregnant women, or in persons with a normal glucose 6 phosphate dehydrogenase (G6PD) activity, this treatment should be followed by a 15-day-course of primaquine (15 mg/day) for *P. vivax/ ovale* infections in order to eliminate liver hypnozoites and to avoid late recurrences. However, even with this combination treatment, relapses are still possible in 15 % of the cases. Then, a higher dosage of primaquine or a longer duration of treatment may be needed (after a specialised advice). For *P. falciparum* infections, the spread of multidrug resistant strains has severely limited the use of chloroquine and sulfadoxine-pyrimethamine (Fansidar®) for non-immune patients. Concerns continue to be expressed about the risks and the tolerance of halofantrine and mefloquine, making their curative use particularly uneasy. Despite its many disadvantages, quinine remains the drug of choice, and its association with doxycycline or clindamycin allows for shortening treatment duration. Recently, Malarone® (a combination of 250 mg of atovaquone and 100 mg of proguanil) has become commercially available in Belgium. In adults, a dose of 4 tablets of Malarone® once daily for 3 days was found to be highly effective and well tolerated against uncomplicated (multidrug resistant) falciparum malaria (27). Semi-synthetic derivatives of artemisinin (like artemether and artesunate) are potent, safe and well tolerated drugs against uncomplicated and complicated falciparum malaria. They are however not yet registered in Belgium, but are increasingly used in Asia and Africa. Because of concerns about the possible emergence of resistance, combination therapies are advocated. Another reason to propose to combine artemisinin with other antimalarials is to reduce the 5% of risk of relapse of P. falciparum infections observed

after artemisinin monotherapy. There is only one fixed-ratio artemisinin-containing combination, lumefantrine with artemether (coartemether; Riamet"), to be given in a 3-day course. This drug is available in Switzerland. It is registered in Europe since 2002, and will be marketed later in the different member-countries. It will then represent a new oral therapeutic option for uncomplicated falciparum malaria.

International recommendations for prevention need frequent updates, according to the changes in the resistance pattern of *P. falciparum.* Options for chemoprophylaxis are limited to a few regimens (chloroquine alone, combination of chloroquine/proguanil, mefloquine, doxycycline, and combination of atovaquone/proguanil), according to visited regions, traveller's age, duration of travel, specific contra-indications, tolerance, and budget (see the WHO guidelines : www.who.int/ith and the Belgian guidelines : www.itg.be). Among other preventive regimens under investigation, primaquine (30 mg once daily) was proven to be effective, safe and particularly well accepted, because only 1 week of post-exposure dosing is needed (28,29). However, the need of predetermination of the G6PD activity may limit its use. Tafenoquine, a newly developed primaquine analogue is highly efficacious and well tolerated in preliminary studies, and has a promising profile in the chemoprophylactic armamentarium (30).

Malaria remains a frequent and potentially life-threatening infection in travellers. Although travel medicine specialists have the feeling that the message of "first exclude malaria" is widely diffused, it is disquieting to observe that delays in the management of imported malaria remains a problem, leading sometimes to deadly complications.

ENTERIC FEVER (TYPHOID AND PARATYPHOID FEVER)

Enteric fever (EF) refers to systemic infection by Salmonella typhi (typhoid fever) or Salmonella paratyphi A, B, or C (paratyphoid fever). The disease affects only humans, through a person-to-person transmission, via the fecal-oral route. Yearly, 33 million cases occur throughout the world, with > 50 % in Asia (31). Almost all cases of EF in industrialised countries are now-travel related (> 80 % in USA in 1997) (32). Travellers to the Indian sub-continent have a 18-fold increased risk of developing EF compared to other destinations (33). The median and maximal incubation time were 10 and 26 days after return in a retrospective study of French travellers (34). Clinical symptoms (fever, cough, abdominal discomfort, rose spots) and laboratory data are not specific enough to establish a diagnosis in travellers, who consult usually early in the course of the disease (34). An initial episode of diarrhoea often has disappeared when fever develops. The final diagnosis of EF is based on the isolation of *S. typhi/paratyphi* in clinical specimens. Blood cultures are positive in 2/3 of cases, while bone marrow cultures yield 90 % of positive results, even under antibiotics. Stool and urine cultures rarely provide the diagnosis (34). Serology (Widal test) is unreliable in clinical practice (34,31). Multidrug resistance (ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole) of *S. typhi* is increasingly reported in India and Vietnam, two popular travel destinations (33). As a consequence fluoroquinolones or third-generation cephalosporins have been proposed as empirical treatment of suspected cases (35). Oral azithromycin (10 mg/kg/day) appears also to be an effective and convenient alternative treatment for uncomplicated typhoid fever, especially in children (36). The recommended treatment duration with these regimens has been 7 to 10 days for travellers. However, in autochthonous individuals living in endemic areas, high cure rates were observed with shorter duration (3-5 days) of fluoroquinolones or ceftriaxone for uncomplicated typhoid fever (37,38). Relapses are reported in 2,5 % of cases even after adequate treatment (31). Recently, decreased susceptibility of *S. typhi* to ciprofloxacin in some Asiatic countries (up to 5 % of the strains) has been reported (39). Therefore, vaccination may become an interesting option. Two types of vaccine are available in Belgium: the parenteral Vi antigen vaccine (Typhim®, Typherix®) and the oral live non pathogenic TY21a vaccine (Vivotif®). These vaccines protect only against S. typhi infection. In a recent meta-analysis, a similar efficacy has been reported for both vaccines, ranging from 64 % to 72 % in endemic regions (40). Vaccination is recommended for adventurous travellers, especially to high-risk areas. Phase 2 studies are currently on-going in Vietnam with a conjugate vaccine against *S. typhi.* Preliminary results are very promising, with protection rates of more than 90% in Vietnamese children between 2 and 5 years old (41).

DENGUE

Dengue infection is caused by any of the 4 different serotypes of the Dengue virus (DEN-1, DEN-2, DEN-3,DEN-4), and is transmitted by day-biting Aedes mosquitoes. This infection represents the most frequent mosquito-borne viral illness, affecting 50-100 million persons per year in the world. The 4 serotypes of Dengue, and their vectors, are distributed throughout tropical and sub-tropical areas, predominantly in south east Asia, and Latin America (42) (see map : http://www.cdc.gov/ncidod/dvbid/dengue/map-distribution-2000.htm). There is evidence that the incidence of dengue is on the increase in travellers (43). Dengue seroprevalence rates of 4,3 % were found in long-term German expatriates returning from endemic areas (44). In a prospective study of short-term Israeli travellers to tropical areas, a dengue seroconversion rate of 6,7 % was observed (45). The risk for clinical dengue fever has been estimated to be at least 0,9/1000 pmt in travellers to Thailand (46). In a recent well-designed prospective study, in which pre- and post-travel dengue seroprevalences were compared after a stay in Asia, the incidence of dengue infection was found to be 36, 9/1000 pmt. The apparent-to-inapparent infection rate was 1:3, indicating that dengue infection remains subclinical in most infected people (47).

Clinically apparent dengue infection, the dengue fever (DF) syndrome, tends to present with less typical symptoms among travellers than among endogenous populations. Non-specific symptoms such as headache, arthralgia and fever predominate, while rash (in only 50% of the cases), sore throat and cough (occurring mostly in children), nausea and vomiting, or generalised lymphadenopathy are less common (48,49). DF is a self-limited disease, with symptoms lasting 5-7 days before abating. Leucocytopenia or thrombocytopenia may suggest the diagnosis, even if not specific nor sensitive. Raised serum aminotransferase levels are a common laboratory feature. Complications occur in 1 % of the symptomatic patients (42,43). Minor haemorrhagic signs may occur and sometimes evolve to a severe bleeding disorder: the dengue haemorrhagic fever (DHF). Some patients may develop a vascular collapse: the dengue shock syndrome (DSS). This severe complication is the result of a massive immune mediated vascular leakage into the third space. DSS is always associated with DHF, and is preceded by severe thrombocytopenia and haemoconcentration. DHF/DSS is quite unusual among travellers (48,49). Risk factors for these complications have not been completely identified, but DHF/DSS seems to be related to a subsequent dengue infection with another serotype, and to the virulence of some viral strains. Exceptionally, other complications such as acute hepatic failure (50) and encephalitis have been reported (51).

Dengue infection goes frequently unrecognised in travellers, because the definitive diagnosis requires a fourfold rise of antibodies in paired sera. Seroconversion occurs at the end of the febrile stage and during early convalescence. Therefore, new diagnostic methods are needed to be used during the early febrile phase. Isolation of the virus on continuous mosquito cell lines is potentially feasible, but its sensitivity is low (50 %), and the procedure requires specialised laboratory facilities. PCR testing for early dengue diagnosis could be useful, but is not yet available for routine use. Moreover, these tests become negative when fever and viremia subside (52,53). Antibody tests based on conventional haemagglutination inhibition (HI) are still considered as the gold standard for dengue diagnosis, but are quite costly and require long delays for confirmation (54). ELISA antibody detection tests are inexpensive, quick and simple to perform, and they are currently the most frequently used diagnostic tools. However, they have several limitations. Although highly specific (> 95 %), IgM ELISA may be negative during the first week of illness, and sometimes as well during subsequent (secondary) infections. Dengue IgM-antibody titers remain raised for about 3 months. IgG ELISA based tests are sensitive, but become positive later. In case of secondary dengue infections there is always a dramatic increase of IgG-antibody titers. However, these tests crossreact with other flaviviral infections, and even with prevaccination against Japanese encephalitis (JE) and/or yellow fever (YF). A false positive antibody response was observed in 20-40 % of healthy travellers vaccinated against JE and/or YF. Therefore, a single positive IgG-ELISA result in a vaccinated traveller, as well as a negative IgM-ELISA result during the first week of illness are both inconclusive for dengue diagnosis. In these cases a second serum sample during convalescence is required to ascertain the diagnosis (55,56).

There is so far no specific treatment for DF. Treatment is symptomatic in uncomplicated cases (avoid aspirin), and supportive in case of complications. In expert hands the mortality of DHF/DSS may decrease from 44 % to 0,2 % (42), but adequate facilities are not always available in endemic regions. Vaccines are being developed against the 4 serotypes, and phase I and II studies are currently ongoing in Thailand (57).

RICKETTSIOSES

Rickettsial infections are vector borne diseases, widely distributed throughout the world. Clinical manifestations may include a rash, adenopathies, and sometimes a generalised vasculitis. There is no clear information about their incidence in the tropics nor in travellers to the tropics. Contacts with infected body lice (vectors of *R. prowazeckii*, agent of epidemic typhus), fleas (vectors of *R. typhi*, agent of murine typhus), or mites (vectors of *O. tsutsugamushi,* agent of scrub typhus) are in general unlikely in travellers, although imported infections have been reported (58-61). In contrast, tick-borne tropical rickettsioses represent a well defined hazard for travellers (62). The most frequent causative agents of "tick bite fever" are *R conori*, responsible for the "fièvre boutonneuse", or Mediterranean spotted fever, and *R. africae* causing the classic African tick typhus. *R. conori* infection is transmitted by dog ticks, presents in an urban and a sporadic form, and is widespread throughout the world, and especially in the Mediterranean basin. *R. africae* is transmitted by cattle ticks, occurs mainly in rural areas and is contracted during out-door activities (walking safari, hunting, trekking) (63). It is distributed throughout sub-Saharan Africa, but contamination occurs most frequently in travellers to the southern part. Incubation is always short (4-10 days), and a tick bite is not always observed or mentioned by the patient. Both infections are generally mild and characterised by fever, inoculation chancre (unique or multiple) called eschar (90-100%), regional adenopathy (90%) and a maculo-papular rash (30-60 %). Serious complications are exceptional (64). Diagnosis is mainly clinical, based on the presence of a typical eschar, and may be confirmed by serological tests (indirect immunofluorescence), specific for *R. conori* infection. Serology is very sensitive and specific, but crossreaction with closely related species (*R. africae)* usually occurs. Treatment with doxycycline rapidly results in clinical cure. Relapse or secondary complications are not observed (64,65).

Other tropical rickettsial infections, like murine typhus (no eschar) or scrub typhus (40% eschar) present with similar clinical manifestations, but occasionally with a more severe clinical course resembling typhoid fever.

KATAYAMA FEVER (ACUTE BILHARZIOSIS OR SCHISTOSOMIASIS)

Schistosomiasis is contracted through contact with fresh (not salt) water harbouring a larval stage of the trematode ("cercaria") emanating from the infected intermediate snail host. It occurs in endemic regions throughout sub-Saharan Africa and some parts of south America and south east Asia (66) (see also map: http://www.who.int/ctd/schisto/epidemio.htm). Most patients with established schistosomiasis are asymptomatic. Katayama fever represents the acute inflammatory/allergic symptoms due to maturing schistosomal larvae and the first eggs deposition (67,68). Typically, symptoms occur 3 to 8 weeks after infection and are consistent with a serum sickness syndrome. Features include fever, myalgia, bronchospasm, and an urticarial rash. The illness may be incapacitating, and sometimes severe (69). A marked eosinophilia is almost always present. Acute schistosomiasis occurs only in a minority of people infected with schistosomiasis, with an estimated rate of clinical illness of 3% to 50% (70-73). Only part of the infected persons experienced a transient itching soon after water contact (swimmers' itch) (72). Symptoms of the Katayama syndrome are non-specific. It is a self-limiting condition, often misdiagnosed as a respiratory viral infection. Diagnosis is likely when a febrile patient presents with a history of a recent exposure to water of river/lake in an endemic area (3-8 weeks prior), bronchopulmonary symptoms and hypereosinophilia, and without another obvious cause that could explain the fever. Diagnosis can only be confirmed after several weeks by serological testing or through the detection of viable eggs (73). Because the Katayama syndrome is the result of an inflammatory response to ovideposition, administration of corticosteroids (20-30 mg/day during at least 3 days) produces prompt symptom relief, and is certainly recommended for serious cases. Praziquantel is now the preferred treatment for schistosomiasis, but its administration (40-60 mg/kg/day during 3 days) does often not improve immediately the Katayama fever symptoms, and even exacerbates them sometimes. In addition, this drug eliminates only the adult worms, and it is recommended to administer a second dose (40 mg/kg one day) one to three months later to eradicate the remaining adult worms emanating from larvae not inactivated by the first treatment (67). The course of the disease may be complicated by the transient exacerbation of the symptoms, or sometimes recurrences, usually when the steroids are

tapered. As diagnosis and treatment of Katayama syndrome are uneasy, and as its course may be severe and unpredictable, it is recommended to obtain specialised advice, when this diagnosis is considered.

The treatment of Katayama syndrome is advisable as an untreated schistosomal infection carries a small risk of severe long-term complications, more specifically transverse myelitis due to embolisation of eggs or adult worms in the spinal cord (74).

REFERENCES

1. Newman RD, Barber AM, Roberts J, Holtz T, Steketee RW, Parise ME. Malaria Surveillance-United States, 1999. *MMWR* 2002; 51.
2. Sabatinelli G, Ejov M, Joergensen P. Malaria in the WHO European Region (1971-1999). *Euro Surveill.* 2001; 6: 61- 65.
3. Van den Ende J, Morales I, Van den Abbeele K, et al. Changing epidemiological and clinical aspects of imported malaria in Belgium. *J Travel Med.* 2001; 8: 19-25.
4. Jelinek T, Schulte C, Behrens R et al. Imported Falciparum malaria in Europe: sentinel surveillance data from the European network on surveillance of imported infectious diseases. *Clin Infect Dis.* 2002; 34: 572-6.
5. Jelinek T, Grobusch M, Harms-Zwingenberger G, Kollaritsch H, Richter J, Zieger B. Falciparum malaria in European tourists to the Dominican Republic. *Emerg Infect Dis.* 2000; 6: 537-8.
6. Steffen R., DuPont HL, Malaria. In: Steffen R, Dupont HL, eds. Manual of Travel Medicine and Health. Hamilton: BC Decker Inc. 1999; 217-60.
7. Oswald G, Lawrence EP. Runway malaria. *Lancet.* 1990; 335: 1537.
8. Gyorkos TW, Svenson JE, MacLean JD, Mohamed N, Remondin MH, Franco ED. Compliance with antimalarial chemoprophylaxis and the subsequent development of malaria: a matched case-control study. *Am J Trop Med Hyg.* 1995; 53: 511-7.
9. Lewis SJ, Davidson RN, Ross EJ, Hall AP. Severity of imported falciparum malaria: effect of taking antimalarial prophylaxis. *Br Med J.*1992; 305: 741-3.
10. Kollaritsch H, Wiedermann G. Compliance of Austrian tourists with prophylactic measures. *Eur J Epidemiol.* 1992; 8: 243-51.
11. Williams A, Lewis DJ. Malaria prophylaxis: postal questionnaire survey of general practitioners in south east Wales. *Br Med J* 1987; 295: 1449-52.
12. Dorsey G, Gandhi M, Oyugi JH, Rosenthal PJ. Difficulties in the prevention, diagnosis, and treatment of imported malaria. *Arch Intern Med.* 2000; 160: 2505-10.
13. Kain KC, Harrington MA, Tennyson S, Keystone JS. Imported malaria: prospective analysis of problems in diagnosis and management. *Clin Infect Dis.* 1998; 27: 142-9.
14. Svenson JE, Gyorkos TW, MacLean JD. Diagnosis of malaria in the febrile traveler. *Am J Trop Med Hyg.*1995; 53: 518-21.
15. Svenson JE, MacLean JD, Gyorkos TW, Keystone J. Imported malaria. Clinical presentation and examination of symptomatic travellers. *Arch Intern Med.*1995; 155: 861-8.
16. Krajden S, Panisko DM, Tobe B, Yang J, Keystone JS. Prolonged infection with Plasmodium falciparum in a semi-immune patient. *Trans R Soc Trop Med Hyg.* 1991; 85: 731-32.
17. Warrell DA. Severe falciparum malaria. *Trans R Soc Trop Med Hyg.* 2000; 94 (S1) : 1-90.
18. Jensenius M, Ronning EJ, Blystad H et al. Low frequency of complications in imported falciparum malaria: a review of 222 cases in south-eastern Norway. *Scand J Infect Dis.* 1999; 31: 73-8.
19. Muentener P, Schlagenhauf P, Steffen R. Imported malaria (1985-95): trends and perspectives. *Bull World Health Organ.*1999; 77: 560-6.
20. Greenberg AE, Lobel HO. Mortality from Plasmodium falciparum malaria in travelers from the United States, 1959 to 1987. *Ann Intern Med.* 1990; 113: 326-7.
21. Milne LM, Kyi MS, Chiodini PL, Warhurst DC. Accuracy of routine laboratory diagnosis of malaria in the United Kingdom. *J Clin Pathol.* 1994; 47: 740-2.
22. Moody A. Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev.* 2002; 15: 66-78.
23. Pieroni P, Mills CD, Ohrt C, Harrington MA, Kain KC. Comparison of the ParaSight-F test and the ICT Malaria Pf test with the polymerase chain reaction for the diagnosis of Plasmodium falciparum malaria in travellers. *Trans R Soc Trop Med Hyg.* 1998; 92: 166-9.
24. Van den Ende J, Vervoort T, Van Gompel A, Lynen L. Evaluation of two tests based on the detection of histidine rich protein 2 for the diagnosis of imported Plasmodium falciparum malaria. *Trans R Soc Trop Med Hyg.* 1998; 92: 285-8.
25. Jelinek T, Grobusch MP, Schwenke S et al. Sensitivity and specificity of dipstick tests for rapid diagnosis of malaria in nonimmune travelers. *J Clin Microbiol.* 1999; 37: 721-3 .
26. Moody A, Hunt-Cooke A, Gabbett E, Chiodini P. Performance of the OptiMAL malaria antigen capture dipstick for malaria diagnosis and treatment monitoring at the Hospital for Tropical Diseases, London. *Br J Haematol.* 2000; 109: 891-4.
27. Bouchaud O, Monlun E, Muanza K et al. Atovaquone plus proguanil versus halofantrine for the treatment of imported acute uncomplicated Plasmodium falciparum malaria in non- immune adults: a randomized comparative trial. *Am J Trop Med Hyg.* 2000; 63: 274-9.
28. Baird JK, Lacy MD, Basri H et al. Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia. *Clin Infect Dis.* 2001; 33: 1990-7.
29. Fryauff DJ, Baird JK, Basri H et al. Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *Lancet.*1995; 346: 1190-3.
30. Shanks GD, Oloo AJ, Aleman GM et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. *Clin Infect Dis.* 2001; 33: 1968-74.
31. Zenilman JM. Typhoid fever. *JAMA.* 1997; 278: 847-850.
32. Ackers ML, Puhr ND, Tauxe RV, Mintz ED. Laboratory-based surveillance of Salmonella serotype Typhi infections in the United States: antimicrobial resistance on the rise. *JAMA.*2000; 283: 2668-73.
33. Mermin JH, Townes JM, Gerber M, Dolan N, Mintz ED, Tauxe RV. Typhoid fever in the United States, 1985-1994: changing risks of international travel and increasing antimicrobial resistance. *Arch Intern Med.*1998; 158: 633-8.
34. Caumes E, Ehya N, Nguyen J, Bricaire F. Typhoid and paratyphoid Fever: a 10-year retrospective study of 41 cases in a parisian hospital. *J Travel Med.* 2001; 8: 293-7.
35. White NJ, Salmonella typhi and paratyphi. In : Yu VL, Merigan TC, Barriere SL, eds. Antimicrobial therapy and vaccines. Baltimore: Williams & Wilkins. 1999: S361-76.

36. Frenck RW, Jr., Nakhla I, Sultan Y et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clin Infect Dis.* 2000; 31: 1134-38.
37. Acharya G, Butler T, Ho M et al. Treatment of typhoid fever: randomized trial of a three-day course of ceftriaxone versus a fourteen-day course of chloramphenicol. *Am J Trop Med Hyg.* 1995; 52: 162-5.
38. Nguyen TC, Solomon T, Mai XT et al. Short courses of ofloxacin for the treatment of enteric fever. *Trans R Soc Trop Med Hyg.* 1997; 91: 347-9.
39. Chitnis V, Chitnis D, Verma S, Hemvani N . Multidrug-resistant Salmonella typhi in India. *Lancet.* 1999; 354: 514-5.
40. Engels EA, Falagas ME, Lau J, Bennish ML . Typhoid fever vaccines: a meta-analysis of studies on efficacy and toxicity. *Br Med J.* 1998; 316: 110-6.
41. Lin FY, Ho VA, Khiem HB et al. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five- year-old children. *N Engl J Med.* 2001; 344: 1263-9.
42. Guzman MG, Kouri G. Dengue: an update. *Lancet Infect Dis.* 2002; 2: 33-42.
43. Jelinek T. Dengue fever in international travelers. *Clin Infect Dis.* 2000; 31: 144-7.
44. Janisch T, Preiser W, Berger A et al. Emerging viral pathogens in long-term expatriates (II): Dengue virus. *Trop Med Int Health.* 1997; 2: 934-40.
45. Potasman I, Srugo I, Schwartz E. Dengue seroconversion among Israeli travelers to tropical countries. *Emerg Infect Dis.* 1999; 5: 824-7.
46. Schwartz E, Moskovitz A, Potasman I, Peri G, Grossman Z, Alkan ML. Changing epidemiology of dengue fever in travelers to Thailand. *Eur J Clin Microbiol Infect Dis.* 2000; 19: 784-6.
47. Cobelens FG, Groen J, Osterhaus AD, Leentvaar-Kuipers A, Wertheim-van Dillen PM, Kager PA. Incidence and risk factors of probable dengue virus infection among Dutch travellers to Asia. *Trop Med Int Health.* 2002; 7: 331-8.
48. Bakker RC, Veenstra J, Dingemans-Dumas AM, Wetsteyn JCFM, Kager PA. Imported Dengue in The Netherlands. *J Travel Med.* 1996; 3: 204-8.
49. Schwartz E, Mendelson E, Sidi Y. Dengue fever among travelers. *Am J Med.* 1996; 101: 516-20.
50. Murgue B, Deparis X, Chungue E, Cassar O , Roche C. Dengue: an evaluation of dengue severity in French Polynesia based on an analysis of 403 laboratory-confirmed cases. *Trop Med Int Health.* 1999; 4: 765-73.
51. Solomon T, Dung NM, Vaughn DW et al. Neurological manifestations of dengue infection. *Lancet.* 2000; 355: 1053-9.
52. Vaughn DW, Green S, Kalayanarooj S et al. Dengue in the early febrile phase: viremia and antibody responses. *J Infect Dis.* 1997; 176: 322-30.
53. Vaughn DW, Green S, Kalayanarooj S et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J Infect Dis.* 2000; 181: 2-9.
54. Guzman MG, Kouri G. Advances in dengue diagnosis. *Clin Diagn Lab Immunol.* 1996; 3: 621-7.
55. Schwartz E, Mileguir F, Grossman Z, Mendelson E. Evaluation of ELISA-based sero-diagnosis of dengue fever in travelers. *J Clin Virol.* 2000; 19: 169-73.
56. Vaughn DW, Nisalak A, Kalayanarooj S et al. Evaluation of a rapid immunochromatographic test for diagnosis of dengue virus infection. *J Clin Microbiol.* 1998; 36: 234-8.
57. Kanesa-thasan N, Sun W, Kim-Ahn G et al. Safety and immunogenicity of attenuated dengue virus vaccines (Aventis Pasteur) in human volunteers. *Vaccine.* 2001; 19: 3179-88.
58. Marschang A, Nothdurft HD, Kumlien S, von Sonnenburg F. Imported rickettsioses in German travelers. *Infection.* 1995; 23: 94-7.
59. Hassan IS, Ong EL. Fever in the returned traveller. Remember murine typhus! *J Infect.* 1995; 31: 173-4.
60. Zanetti G, Francioli P, Tagan D, Paddock CD, Zaki SR. Imported epidemic typhus. *Lancet.* 1998; 352: 1709.
61. Watt G, Strickman D. Life-threatening scrub typhus in a traveler returning from Thailand. *Clin Infect Dis.* 1994; 18: 624-6.
62. Raoult D, Fournier PE, Fenollar F et al. Rickettsia africae, a tick-borne pathogen in travelers to sub-Saharan Africa. *N Engl J Med.* 2001; 344: 1504-10.
63. Fournier PE, Roux V, Caumes E, Donzel M, Raoult D. Outbreak of Rickettsia africae infections in participants of an adventure race in South Africa. *Clin Infect Dis.* 1998; 27: 316-23.
64. Jelinek T, Loscher T. Clinical features and epidemiology of tick typhus in travelers. *J Travel Med.* 2001; 8: 57-9.
65. Jensenius M, Hasle G, Henriksen AZ et al. African tick-bite fever imported into Norway: presentation of 8 cases. *Scand J Infect Dis.* 1999; 31: 131-3.
66. Ross AG, Bartley PB, Sleigh AC et al. Schistosomiasis. *N Engl J Med.* 2002; 346: 1212-20.
67. Doherty JF, Moody AH, Wright SG. Katayama fever: an acute manifestation of schistosomiasis. *Br Med J.* 1996; 313: 1071-72.
68. Nash TE, Cheever AW, Ottesen EA, Cook JA . Schistosome infections in humans: perspectives and recent findings. NIH conference. *Ann Intern Med.* 1982; 97: 740-54.
69. Cooke GS, Lalvani A, Gleeson FV, Conlon CP. Acute pulmonary schistosomiasis in travelers returning from Lake Malawi, sub-Saharan Africa. *Clin Infect Dis.* 1999; 29: 836-9.
70. Whitty CJ, Mabey DC, Armstrong M, Wright SG, Chiodini PL. Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country. *Trans R Soc Trop Med Hyg.* 2000; 94: 531-4.
71. Day JH, Grant AD, Doherty JF, Chiodini PL, Wright SG. Schistosomiasis in travellers returning from sub-Saharan Africa. *Br Med J.* 1996; 313: 268-9.
72. Colebunders R, Verstraeten T, Van Gompel A et al. Acute Schistosomiasis in Travelers Returning From Mali. *J Travel Med.* 1995; 2: 235-8.
73. Visser LG, Polderman AM, Stuiver PC. Outbreak of schistosomiasis among travelers returning from Mali, West Africa. *Clin Infect Dis.* 1995; 20: 280-5.
74. Blanchard TJ, Milne LM, Pollok R, Cook GC. Early chemotherapy of imported neuroschistosomiasis. *Lancet.* 1993; 341: 959.