#### abstract





The number of international travellers is steadily increasing, paralleled by the number of persons with travel-related diseases. Fever in the returning traveller should always raise suspicion of severe and potentially life-threatening infections. Therefore, physicians should be familiar with the most common syndromes, relevant diagnostic procedures, optimal treatment regimens, and referral criteria. This review gives a general overview of the pathogens causing fever in the returning traveller, their clinical presentation, and standard management procedures.

*Key words: fever, travel, older adults, tropical diseases, vaccination* 

## Fever in the Returning Traveller

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#### Introduction

This review gives a general overview of the pathogens causing fever in the returning traveller, the clinical presentation of common diseases, and standard management procedures. A few major diseases with specific tropical distribution are also briefly discussed. An overview of the current magnitude of the phenomenon is given. Finally, specific characteristics of the older adult population that might affect the risk of diseases and preventive measures before departure are briefly analyzed.

#### Magnitude of Travel and Travel-related Diseases

International travel has rebounded since the attacks of September 11, 2001, and is steadily increasing despite a variety of global health crises. In 2004, 763 million people crossed international borders, reflecting an increase of 73% over the course of 15 years, and the forecast for 2020 is to reach 1.6 billion international tourist arrivals world-wide.<sup>1</sup> In Western countries, retired older adults are usually in good health and have enough economic resources to travel to distant countries to find different climate and cultural conditions.

Health problems are self-reported by 22–64% of travellers to the developing world.<sup>2</sup> The severity varies greatly: most are mild, self-limited illnesses such as diarrhea, respiratory infections, and skin disorders that would be seen at a primary care outpatient service; however, up to 8%, a total of 4 million persons, are ill enough to

require acute hospital inpatient care either while abroad or on returning home.<sup>2-4</sup>

Fever in the returning traveller should always raise suspicion of severe and potentially life-threatening infections. In the recently published Geosentinel study,<sup>5</sup> deaths were registered among patients with a systemic febrile illness, mainly due to severe and complicated malaria, pulmonary embolism, pneumonia, and pyogenic abscess.<sup>5</sup> Therefore, physicians do need to be familiar with the most common travel-associated syndromes, relevant diagnostic procedures, optimal treatment regimens, and referral criteria. Given this, the need for continued education and training in travel medicine is clear and substantial.

#### Clinical Presentation and Standard Management Procedures

A few large studies, although unable to provide a comprehensive picture, constitute the bases for current understanding of morbidity profiles among ill returned travellers.<sup>5–8</sup> Nevertheless, the practices for care of travellers with fever and accompanying symptoms are poorly standardised. A syndromic approach is appropriate for a clinician to devise differential diagnoses of diseases causing fever in the returning traveller.

#### Initial Clinical Assessment

In the assessment of a returning traveller, the physician should consider geographical, seasonal, environmental, cultural, and chronological factors.

A detailed travel history is essential because the risk of acquiring a travelrelated infection depends on the precise geographic location and the length of stay at each destination.<sup>8,9</sup> Specific regions visited within each country should be determined because some infections are focally transmitted and risk is only present when travelling in endemic areas.<sup>9,10</sup> Friedman et al. have recently shown that travel destinations to the developing world are associated with the probability of the diagnosis of certain diseases and suggest that diagnostic approaches and empiric therapies can be guided by these destination-specific differences.<sup>5</sup> For example, systemic febrile illness was found disproportionately among travellers from sub-Saharan Africa or Southeast Asia.5

It is important to determine the reason for travel because it may affect the duration of travel, the likelihood of travel in rural or urban areas, and the likelihood of sexual contact with local inhabitants.<sup>11</sup> Because the risk of acquiring a tropical infection is affected by one's activities during travel, and because many tropical diseases present with nonspecific signs and symptoms, the physician needs to know the patient's activities to provide a correct diagnosis. For example, walking in forests or rural settings increases the chance of exposure to insect vectors' bites, and bathing in lakes or rivers to leptospires or schistosomes.8 Eating certain foods or drinking unsafe water may cause food-borne illnesses.

Moreover it is important to know the health of the patient before travel because the presence of underlying illnesses and pretravel immunizations and chemoprophylaxis can affect the susceptibility to infections.

Finally, the physician needs to know the precise date of the onset of the fever and the date of the return to define the likelihood of a disease relative to its incubation period (see Table 1). A travel history is particularly critical if the patient presents with a febrile syndrome because the failure to associate a syndrome with travel may delay diagnosis and lead to adverse outcomes. In the Geosentinel

Table 1: Most Common Causes of Fever Related to Incubation Periods			
<b>Short</b> (<10 days)	<b>Medium</b> (10–21 days)	<b>Long</b> (>21 days)	
Dengue fever	Viral hemorrhagic fevers	Viral hepatitis	
Enteric fevers	Typhoid fever	Visceral leishmaniasis	
Rickettsioses	Rickettsioses	Malaria	
Borreliosis	Brucellosis	Amoebic liver abscess	
Plague	Malaria	Acute HIV infection	
Malaria	Leptospirosis	African trypanosomiasis	
Yellow fever	African trypanosomiasis	Tuberculosis	
	Q fever	Katayama fever	
		Acute linfatic filariasis	

series 36% of travellers presented with an illness 1 month or more after returning home.<sup>5</sup>

#### **Physical Examination**

A thorough physical examination of the patient can guide the physician toward the correct diagnosis. The initial step is to recognise possible signs of life-threatening conditions that warrant immediate and intensive care (see Table 2).

After the general status of the patients has been assessed, the physician should identify signs and symptoms of organ involvement as a basis for a syndromic approach to the diagnostic and treatment procedures (see Table 3).

## Syndromic Classification of Fever Cases

## Systemic Febrile Illnesses

The most frequent presenting condition of travellers with fever is a systemic illness with no organ involvement. Malaria, dengue, leptospirosis, typhoid fever, and rickettsial infections are the causative agents in most of the patients with this condition. Still, a specific etiologic diagnosis remains elusive in up to 40% of cases with systemic febrile illness.<sup>5,7,8,12</sup>

## Malaria

Overall, malaria is the most frequent sin-

gle disease diagnosed in travellers with fever from the developing world.<sup>5</sup> This is particularly true among travellers from sub-Saharan Africa, where the risk for infection is estimated at 1.5–2.4% per month of exposure in the absence of chemoprophylaxis.<sup>13</sup> Of the four species of plasmodia *P. vivax* is the most common, but P. falciparum results in the most serious illness. Almost 90% of infected people with P. falciparum return from Africa and approximately 90% become symptomatic within 2 months of departure from the endemic area.<sup>10</sup> Most cases of malaria in travellers are due to lack of or inappropriate chemoprophylaxis, including early termination of a chemoprophylactic regimen due to adverse events.<sup>14,15</sup> A typical presentation consists of the abrupt onset of chills followed by high fever, profound malaise, myalgia, and severe headache.16,17 Gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea) may occur in up to 25% of patients. Respiratory symptoms, though not usually considered typical signs of uncomplicated malaria, may occur in up to 5% of imported malaria cases.<sup>18</sup> Severe falciparum malaria may result in neurological deterioration, renal failure, and pulmonary edema, all three leading to death.<sup>19</sup> Diagnosis is based on the demonstration of parasites in thick and



thin blood films. Treatment guidelines are available for both complicated and uncomplicated malaria.<sup>19,20</sup>

#### Dengue

Dengue (Figure 1) has been reported in travellers since the 1980s, and it now appears to occur more frequently than malaria among travellers returning from any region except Africa and Central America. It is particularly frequent among travellers returning from Southeast Asia and the Caribbean.<sup>5</sup> Coinciding with this trend is the spread of the disease to new areas in South and Central America, the development of new diagnostic tools, and the increased awareness of the disease.<sup>21</sup> The infection is transmitted by the day-biting Aedes mosquito,<sup>22,23</sup> and symptoms typically develop after a short incubation period, from 3-10 days. Patients with dengue fever usually present with abrupt onset of fever, frontal headaches, retro-orbital pain, severe myalgias, and transient macular rash.<sup>24</sup> Leucopoenia and mild thrombocytopenia are frequent but nonspecific findings.<sup>23</sup> Dengue hemorrhagic fever is the potentially fatal, immune-mediated complication of repeated episodes of infection with different serotypes.<sup>21</sup> Diagnosis is made clinically and confirmed with virus isolation, dengue virus antigens, increased IgM antibodies, or a fourfold increase in IgG between acute- and convalescent-phase serum samples.<sup>25</sup> Treatment consists of supportive measures.

#### **Rickettsial Infections**

Rickettsial infections are a frequent cause of fever among travellers returning from sub-Saharan Africa. They are vectorborne illnesses usually carried by ticks. The many agents present with similar syndromes: Mediterranean spotted fever, African tick typhus, Rocky Mountain spotted fever. The emergence of *Rickettsia africae* in recent years in southern Africa has been well documented in several single-site studies.<sup>26,27</sup> After an incubation of 1–2 weeks, fever arises concurrent with headaches and myalgia. A macular or maculopapular rash may develop 5–6 days after the onset of fever in many,

#### Table 2: Red Flags at Initial Evaluation of Travellers with Fever

Signs and symptoms	Differential diagnosis
Fever + petechiae or hemorrhagic lesion	Septicemia (meningococcal), viral hemorrhagic fevers, dengue fever, leptospirosis, severe malaria
Fever + severe headache and rigor	Meningitis, viral encephalitis, severe malaria, dengue fever, leptospirosis, african trypanosomiasis, typhoid fever
Fever + jaundice	Yellow fever, hemorrhagic fevers, viral hepatitis, complicated typhoid fever, leptospirosis, severe malaria ("blackwater fever")

but not all, cases: it involves palms, soles, and face. Up to one-third of patients can present with diarrhea. Lymphadenopathy is common, and a few patients develop hepatosplenomegaly. The diagnosis of rickettsial disease usually is confirmed with serology. Doxycycline is the treatment of choice.

#### Leptospirosis

Leprospirosis, mainly due to spirochete Leptospira interrogans, has a worldwide distribution and is a possible cause of fever among travellers.<sup>28</sup> Exposure occurs while bathing, rafting, gardening, farming, or drinking water contaminated with the urine of infected animals or people. Clinical presentation of leptospirosis can be distinguished into two syndromes. After an incubation of 1-3 weeks the anicteric leptospirosis, in 90% of cases, presents with chills, fever, headache, nausea, vomiting, and myalgias. Conjunctival suffusion, maculopapular rash and hepatosplenomegaly may sometimes be noted. Five to 10% of the cases develop Weil's syndrome, characterized by fever, jaundice, renal failure, meningitis, hypotension, acute respiratory distress syndrome, and pulmonary hemorrhages.<sup>29</sup> Diagnosis is usually made in the first week of the disease through culture of blood or cerebrospinal fluid; after 10 days the bacteria can be found in urine. Serology can contribute to the diagnosis. Penicillin or doxycycline are the treatments of choice.

## Typhoid Fever

Typhoid fever still represents a primary contributor to systemic febrile illness among travellers, especially those returning from south central Asia.5,25,30 The causative agents Salmonella typhi or, less commonly, paratyphi, are usually acquired by contaminated food or water. Individuals present with increasing fever in a step-ladder pattern over 1-2 weeks, headache, abdominal discomfort, and cough. Although diarrhea may occur early in the course of the disease, it often resolves before fever, and constipation is a usual complaint on presentation. In 30–50% of patients pink and fleeting spots on the chest or abdomen are found. Diagnosis is achieved by isolation of the organism in cultures of blood, stool, urine, bone marrow, and duodenal aspirates. Fluoroquinolone antibiotics are the treatment of choice. Because of the efficacy of the vaccines is approximately 70%, typhoid fever should be suspected even in patients who have been immunized.<sup>31</sup>

## **Respiratory Tract Infections**

There is no generally accepted definition for respiratory syndromes: cough with runny nose, or either of these with any one of headache, fever, or shortness of breath are widely used for study purposes. Respiratory diseases represent a frequent,<sup>32</sup> potentially life-threatening<sup>33</sup> health problem in travellers, and are a reason for concern due to the possibility of importation of infections such as influenza, diphtheria, or tuberculosis.<sup>34–36</sup> In most analyses respiratory

# Table 3: Differential Diagnosis of Fever with Specific Accompanying Signs or Symptoms in the Traveller

Signs and symptoms	Differential diagnosis
Fever + splenomegaly	Malaria, visceral leishmaniasis, brucellosis, borreliosis, acute schistosomiasis
Fever + hepatomegaly	Liver abscess, hepatitis, visceral leishmaniasis, acute schistosomiasis, echinococcus cysts (broken)
Fever + localized lymphadenopathy	Dengue, tuberculosis, infectious mononucleosis, African trypanosomiasis, rickettsioses, sexually transmitted infections, Hodgkins lymphoma
Fever + generalized lymphadenopathy	Acute HIV infection, African trypanosomiasis, rickettsial diseases, dengue and other arbovirus infections, Epstein- Barr Virus, Cytomegalovirus, lymphoma, leukemia, plague
Fever + skin lesions	Dengue fever and other arbovirus infections, rickettsial diseases, secondary syphilis, acute HIV infection, acute schistosomiasis, exanthematic infections (measles)
Fever + single skin lesion	Rickettsioses, African trypanosomiasis

tract infections (RTI) rank third after travellers' diarrhea and malaria among all infectious problems of the travellers, contributing to approximately 10% of fever cases or more.<sup>18,37–39</sup> Steffen estimated the monthly incidence of acute RTI to be 1,261 per 100,000 travellers.<sup>32</sup> The incidence of RTI is similar in developing and developed nations. In a classic study comparing incidence rates in travellers to different areas, RTI occurred in 3.7 per 1,000 travel days to Latin America, 3.5 per 1,000 to Oceania, and 3.1 per 1,000 to the Caribbean.<sup>40</sup> Decision algorithms for RTI in travellers are proposed but not yet validated (see Figure 2).41 Upper respiratory tract infections should effectively be distinguished from lower ones, to anticipate causative agents and guide treatment decisions. Complications requiring specific treatment should be early identified.

#### Gastroenteric Syndrome

Travellers' diarrhea, the most common travel-related illness, is accompanied by fever in a minority of cases.<sup>2</sup> Intestinal diseases due to helmints or protozoa do not present with fever. However, some organisms such as shigella, salmonella, *Entamoeba histolytica* or *Balantidium coli* can invade the mucosa of the bowels, causing dysentery, which is defined as diarrhea with blood and fever.<sup>42</sup> Diagnosis is made by collecting stool samples that are cultured for pathogenic organisms.

#### Neurological syndromes

The main cause for neurological conditions in returning travellers is generally due to one of four syndromes: meningitis; meningoencephalitis; encephalomyelitis; or brain abscesses.

An algorithm for differential diagnosis in returned traveller with headache or consciousness modifications should first include exclusion of malaria for those coming from endemic areas. The presence of focal neurological signs or the history of convulsions warrants the performance of a brain CT. In presence of clinical signs of meningitis, biochemical and microbiological investigations of the CSF are an essential component of the diagnostic procedure. The most frequent cause for neurological disease in returning travellers is meningococcal meningitis. After an incubation period of 1-3 days it presents with high fever, headache, vomiting, rigor, and sometimes maculopapular skin rash. Several agents may cause encephalitis in travellers, such as the Japanese encephalitis virus and the virus of rabies, or protozoa of the species *Trypanosoma*. Poliomyelitis should be ruled out in travellers with a myelitic syndrome. Finally, signs of neurological involvement are present in severe forms of systemic febrile illnesses such as typhoid fever, HIV infection, yellow fever, leptospirosis, and rickettsial infection.

#### Fever and Hepatitis

Hepatitis A and, with an increasing trend, hepatitis E are the most common diagnoses in febrile travellers with acute hepatitis. Both infections are acquired by the fecal-oral route. Symptomatic hepatitis A infection occurs in 3-6 out of 1,000 travellers per month of stay in resort areas and in up to 20 out of 1,000 travellers per month of stay in rural areas in endemic countries.43 After an incubation period of 2-6 weeks, fever nausea, vomiting, and anorexia occur. Sometimes diarrhea, abdominal pain, and severe malaise may be observed. Jaundice may be absent. Hepatitis A is usually self-limiting but in very few cases may develop a fatal form. The hepatitis A vaccine is safe and highly efficacious, with seroconversion rates of up to 100%.44 Yellow fever is a rare cause of fever and hepatitis among travellers, which is vaccinepreventable as well.

## Fever and Other Clinical Signs

Table 3 briefly reports a list of common diseases that should be considered in the differential diagnosis of travellers with fever and specific accompanying signs or symptoms.

## The Older Traveller

Specific factors associated with aging that may represent a risk for acquisition of an infection abroad have been identified. Older adults, together with infants, pregnant women, disabled persons, and those with pre-existing diseases are considered at increased health risks associated with travel.<sup>46</sup> They should always seek medical advice before departure. At the travel clinic, the older traveller (usually defined as a person over 65 years of age) should be asked about chronic illnesses (mainly cardiovascular disorders, diabetes mellitus, chronic respiratory diseases, and renal insufficiency) and any chronic condition requiring frequent medical intervention or medicines that could represent a risk factor for acquiring infections or worsen previous diseases. In the study by Driessen et al., persons with insulindependent diabetes mellitus travelling to tropical countries had more frequent metabolic problems when they were abroad.<sup>47</sup> Besides that, older adults should be aware of medications that could interact with antibiotics used for prophylaxis or therapy of tropical diseases. For example, trimethoprim-sulfamethoxazol potentiates oral hypoglycemics, while quinolones prolong the half-life of agents such as theophylline.48 Recommendations should include specific environments to be avoided by older individuals, such as high altitudes or very hot or very cold climates. In the case of journeys to hot climates, older adults are more prone to heat stress because they do not adjust as well as young people to sudden changes in temperature; they are more likely to have a chronic medical condition that upsets normal body responses to heat; and they are more likely to take medicines that impair the body's ability to regulate its temperature or that inhibit perspiration.<sup>49</sup> In addition, other general recommendations such as a light diet including easily digestible food, avoidance of drugs or alcohol abuse, and limiting sun expose is useful advice for older travellers.

The issue of travel vaccines for older adults is a very important subject to address before departure. The recommendation for vaccination in general follows that for younger people, taking into consideration the area to be visited and





previous immunization status. However, it must be remembered that older adults have a decrease in the quantity and quality of immune response, mostly cell-mediated immunity, which is present even in healthy individuals.<sup>48,50–52</sup> This condition increases susceptibility to infectious diseases, specially those that an older individual could acquire for the first time in tropical countries during their travels. In general, antibody response tends to be slower (and this may have implications on the timing of pretravel vaccination) and seroconversion rates are lower in groups of older adults. However, data on protective efficacy of vaccines among older adults in developed countries is very limited since the majority of vaccine studies are done on children or young adults from endemic countries. In the case of hepatitis A vaccination, significantly lower peak titres are reached after vaccination in older persons, but the clinical significance of this is unknown since attained serum titres are still higher than those required for protection.53 Lower titres were also described for older persons vaccinated with purified Vi polysaccharide parenteral typhoid fever vaccine in Nepal,<sup>54</sup> against hepatitis B,<sup>55</sup> and against rabies.<sup>56,57</sup> On the other hand, Japanese people age over 60 years who lived in nonendemic areas showed a seroconversion rate similar to those of high school students after vaccination for Japanese encephalitis.<sup>58</sup> There are no studies that have specifically evaluated the serologic response to yellow fever vaccine among older persons, but many others have described a higher rate of serious adverse reactions after vaccination of older adults. In several countries the use of 17 D yellow fever vaccine was associated with higher rates of hospitalization and death in vaccinated individuals aged 65 years or more.59-61 Therefore, it is strongly recommended that, for older travellers, the risk of serious adverse reactions associated with vellow fever vaccination is evaluated against the risk of severe disease and death due to yellow fever infection when abroad.

#### **Key Points**

A detailed travel history, focusing on precise geographic location, the length of stay at each destination, and reasons for travel, is essential.

Malaria, dengue, leptospirosis, typhoid fever, and rickettsial infections are the causative agents in most cases of fever among travellers.

The diagnostic approach to the older traveller returning with fever does not significantly differ from the approach to younger ones; however, note that older adults have a higher risk of severe forms of tropical infections (i.e., malaria) that could be associated with higher fatality rates.

Recommendations for travel vaccines do not vary for older travellers, but protection rates may be lower (hepatitis A, typhoid), and severe adverse events more frequent (yellow fever).

Travellers in general but older adults in particular should have a medical examination upon return, especially in presence of chronic diseases, development of symptoms during travel (mainly fever, persistent diarrhea, vomiting, jaundice, urinary disorders, skin disease, or genital infection), exposure to infectious diseases, or travel periods of more than 3 weeks in a developing country.46 The diagnostic approach to the older traveller returning with fever should essentially be the same as for younger persons. However the health-care provider must be aware that older persons, especially those with chronic diseases, have a higher risk of severe forms of tropical infections that could be associated with higher fatality rates. This feature has been described for respiratory diseases,62 hepatitis A,63 and typhoid fever,<sup>64</sup> but mainly for malaria. Mühlberger et al. evaluated the risk of severe malaria associated with aging. In this study, which compared the clinical course of 78 patients age over 60 years versus 1,103 patients under 60 years with falciparum malaria, older patients had a risk of death and cerebral complication that were, respectively, 5.74 and 3.29 times greater than younger patients.65

Other infections not necessarily associated with travel may be the cause of fever in the returning older traveller. This possibility should be considered to avoid delayed diagnosis and missed treatment of potentially dangerous conditions. Another group of infections whose risk is frequently underestimated among older adults who that travel is sexually transmitted infections (STI), including HIV. It is estimated that about 10% of people diagnosed with AIDS in the United States are age 50 and older.<sup>66</sup> Therefore education and prevention messages on STI/HIV should be included in counselling before departure and STI should be ruled out in the returning older traveller with fever.

#### Conclusion

Older adults who receive correct medical advice before departure are likely to have a lower risk of experiencing medical problems or acquiring infections abroad. In the older traveller returning with fever, the standardized approach used to evaluate younger persons is appropriate; however, special attention should be given to rapid diagnosis and treatment of potentially deadly conditions, in particular falciparum malaria, since the lethality rate is usually higher in this age group.

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#### Fever in the Returning Traveller

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