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Fever in travelers returning from tropical areas: prospective observational study of 613 cases hospitalised in Marseilles, France, 1999-2003

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Summary Background: Febrile travelers may pose a diagnostic challenge for Western physicians who are frequently involved in the assessment of these patients but unfamiliar with tropical diseases. Evaluation of this situation requires an understanding of the common etiologies, which are associated with the demographics of travelers and the destinations.

Methods: We conducted a 5-year prospective observational study on the etiologies of fever in travelers returning from the tropics admitted to the infectious and tropical diseases unit of a university teaching hospital in Marseilles, France.

Results: A total of 613 patients were enrolled, including 364 migrants (59.4%), 126 travelers (20.6%), 37 visitors (6%), 24 expatriates (3.9%), and 62 patients (10.1%) who could not be classified. Malaria was the most common diagnosis (75.2%), with most cases (62%) acquired by migrants from the Comoros archipelago and who had traveled to these islands to visit friends and relatives. Agents of food-borne and water-borne infections (3.9%) and respiratory tract infections (3.4%) were also frequently identified as the cause of fever. Other infections included emerging diseases such as gnathostomiasis, hepatitis E infection and rickettsial diseases, as well as common infections or exotic diseases.

Conclusions: Although we have identified here various causes of imported fever, 8.2% of the fevers remained unexplained. An improved approach to diagnosis may allow for the discovery of new diseases in travelers in the future.

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Millions of people from industrialized countries travel abroad and visit tropical developing countries every year. In spite of recent international problems such as the 2003 SARS epidemic, terrorist attacks, and the Iraq conflict, the popularity of international travel continues to grow, and short-term tourism data for the first half of 2004 confirms the upward trend already evident by the end of 2003.¹ During their trips, travelers expose themselves to various illnesses including routine diseases acquired while traveling, as well as infectious or tropical diseases directly related to the travel.² It has been estimated that up to 50% of travelers visiting developing countries experience a health problem related to their trip.² Furthermore, 3-11% of travelers to tropical areas report a febrile illness on their return.³ This may pose a diagnostic challenge for Western physicians who are frequently involved in the assessment of these patients but unfamiliar with tropical diseases. Thus, patients with fever after returning from the tropics are often admitted to the hospital.³ Evaluation of this situation requires an understanding of the common etiologies, which are associated with the demographics of travelers and the destinations. We undertook a prospective study to analyze the cause of fevers in travelers returning from tropical areas and admitted to the Infectious and Tropical Diseases Unit at the North University Hospital in Marseilles, France, in 1999-2003.

Patients and methods

Study patients were either admitted directly or referred to the Infectious and Tropical Diseases Unit at the North University Hospital in Marseilles, France, from 1 January 1999 to 31 December 2003. The unit was originally located at the Houphouët-Boigny Hospital. When this hospital closed by the end of 2000, the unit moved to the North Hospital, which is located however, near the previous one. The North Hospital is an 800-bed university-affiliated teaching hospital, and the Tropical Diseases Unit is currently the reference center for tropical diseases in Marseilles, southern France. Only adults and children older than 15 years old are hospitalized in this unit. Younger children are hospitalized in the pediatric unit.⁴ Data were collected prospectively in medical records, and included a standard questionnaire completed by medical students and attending physicians. Patients were included in the study if they were hospitalized with fever during the study period, and had a history of travel and/or residence in a tropical

country in the 6 months prior to admission or claimed that their symptoms were related to a travel with no limit of time. All investigations were ordered at the discretion of the attending physician. However, in 2002 a systematic procedure for laboratory investigation was used for all patients (C. Foucault, unpublished). The benefit of such a procedure will be discussed elsewhere.

Patients were classified as 'travelers', 'expatriates', 'migrants' and 'visitors'. We defined travelers, people born and living in France or in Europe whose illness was acquired when they were outside of the country for the purpose of tourism and/or business. 'Expatriates' were those who were born in metropolitan France or in Europe and whose illness was acquired while they were living in a tropical country for the purpose of work. 'Migrants' were those who were born overseas, were permanently residing in metropolitan France at the time of admission, and whose illness was acquired when they returned to tropical countries. Finally, 'visitors' were those who were born and were living outside France and whose illness was acquired while they were staying in a tropical country including their own country, and diagnosed while they were visiting France. Countries were assigned the following broad regional classification if they were situated within the following areas: North Africa; sub-Saharan Africa including West Africa, East Africa, Central Africa, Southern Africa; Indian Ocean including the Union of the Comoros (formerly named Federal Islamic Republic of the Comoros), Mayotte Island (French territory) and Madagascar; Asia including the Middle East, Southeastern Asia, Central Asia and the Indian subcontinent; Oceania; Latin America including Central and South America; and the West Indies.

For all patients included in the study the variables collected are listed below: age; sex; country of origin; country of current residence; travel history; antimalarial chemoprophylaxis; time interval between the onset of fever and admission to hospital; time interval between date of return of and onset of fever; and principal diagnosis at discharge. For malaria cases, the regimen used to treat the patients was recorded. Diagnoses were established by demonstration of microorganism(s) in a clinically relevant specimen or by seroconversion to an infectious disease agent that was considered to be responsible of the travel-related illness. If a specific organism could not be identified, a clinical diagnosis was

assigned. Malaria cases were recorded as uncomplicated or severe according to the WHO definition.⁵

By reviewing medical records, information was recorded on a standard format and analysed by Epi Info, version 6 (Centers for Disease Control and Prevention, Atlanta, USA). Statistical significance was determined by use of the χ^2 test and the Fisher exact test.

Results

Epidemiology

In total, 613 patients were hospitalised with fever after returning from tropical areas in our unit from 1 January 1999 to 31 December 2003. A total of 165 patients were hospitalised in 1999, 113 in 2000, 109 in 2001, 114 in 2002, and 112 in 2003. The patients included 352 men and 261 women (sex-ratio, 1.35). Women (mean age, 34.7 years) were younger than men (mean age, 37.9 years old) ($p < 0.002$). The mean age of the patients was higher in 2003 (40.5 years) than in previous years (34.7–36.6; $p < 0.006$). The median duration of hospitalisation was 5 days (1–37 days). The interval between return to (or arrival in) France and hospital admission was determined for 203 patients. The duration of this interval had a mean of 30.5 days \pm 90 (0–832), and was found to be 17 days for 75% of these patients. The interval between the onset of symptoms and hospital admission was determined for 203 patients. The duration of this interval had a mean of 10 days \pm 28 (0–239), and was found to be 9 days for 75% of these patients.

Among the patients included in this study, 364 were 'migrants' (59.4%), 126 were 'travellers' (20.6%), 37 patients were 'visitors' (6%), 24 were expatriates (3.9%), and 62 patients (10.1%) lacked data to be classified. Among the migrants, people originated from the following areas: Indian Ocean (mainly the Comoros archipelago, 84%); Northern Africa (1.4%); Western Africa (9%), particularly Senegal (4.1%) and Ivory Coast (2.8%); Central Africa (2.5%); and India (0.3%).

The geographical region to which the patients had travelled or were coming from included Indian Ocean (55%) mainly the Comoros archipelago (53%), Western Africa (21.7%), Central Africa (8.8%), South-eastern Asia (3.6%), Central Asia and the Indian subcontinent (3.3%), Northern Africa (1.6%), South America (1.3%), Eastern Africa (0.8%), Oceania (0.5%), Southern Africa (0.3%), North-America (0.3%), West Indies (0.3%), and Central America (0.2%).

Diagnoses

Malaria was the most common diagnosis among our 613 febrile returned patients ($n = 461$; 75.2%). 62% of malaria cases were acquired in the Comoros archipelago, 31.5% in the African mainland, 2.2% in Madagascar, 1.5% in Asia and 0.4% in South America. No malaria cases were reported from Northern Africa, North and Central America, and the West Indies. Depending on the geographic region to which the patients had travelled or were coming from, the proportion of malaria as the cause of fever varied. Malaria was the main diagnosis in patients returning from the Comoros Archipelago, Madagascar and the African Mainland. A total of 286 malaria cases were diagnosed among 324 patients (88.3%) who had returned from the Comoros Archipelago and 10 malaria cases were diagnosed among 11 travellers who had returned from Madagascar. A total of 145 malaria cases were diagnosed among 204 patients returned from the African mainland (71%) including (i) 100 cases among 133 patients (75%) returning from Western Africa, (ii) 40 cases among 54 patients (74%) returning from Central Africa, (iii) 4 cases among 5 patients (80%) returning from Eastern Africa, and (iv) 1 case among the 2 patients returning from Southern Africa. On the other hand, 2 cases of malaria were diagnosed among 8 patients (25%) returning from South America; 7 cases among 42 patients (16.6%) returning from Asia. Data were not recorded for 13 patients. Thus, febrile patients who returned from the Comoros archipelago or the African mainland were significantly more likely to present with malaria (OR, 14.2; 95% CI, 7.9–25.6; $p < 0.0001$).

Based on self reports available for 304 (94%) of 324 patients who had returned from the Comoros Archipelago, it was possible to determine that 64.5% of them used chemoprophylaxis: chloroquine (63.8%), chloroquine-proguanil (24%), proguanil (5.3%), mefloquine (6.4%), and doxycycline (0.5%). Nevertheless, 55.4% discontinued their medication prematurely or took it irregularly (data available for 177 cases). Only one patient took a recommended chemoprophylaxis, mefloquine, regularly during and after the trip. Among 213 patients who had returned from malaria-endemic areas other than Comoros Archipelago, 51.2% used a chemoprophylaxis ($p = 0.005$). Poor compliance was noted for 41.2% of them (compared with 55.4% within Comorians; $p = 0.02$). Also, chloroquine regimen was used less frequently (25.4%) by this categories of patients, compared to those who had returned from Comoros ($p < 0.0001$).

Among all groups of patients with malaria whose chemoprophylaxis use was available ($n=427$), 243 (56.9%) took a chemoprophylaxis, compared to 59 of 90 (65.6%) patients with diagnoses other than malaria. The difference is not significant. However, data were lacking for 32% of patients with a final diagnosis other than malaria, compared to 6% in the malaria group.

Of 461 malaria cases, 421 were due to *Plasmodium falciparum*, and consisted of 401 uncomplicated cases, 17 severe cases including 1 death, and 3 cases of hyperreactive malaria syndrome. Of the 286 patients who had returned from the Comoros Archipelago with malaria, *P. falciparum* was the most common species identified, alone (88.8%) or in association with other *Plasmodium* spp. (1.7%). *P. vivax* (5.9%) and less frequently *P. ovale* (3.1%), and *P. malariae* (0.3%) were also identified. *P. falciparum* was the predominant species identified in cases of malaria acquired in other areas. However, patients who had returned from the Comoros Archipelago developed severe malaria less frequently than non-Comorians (3/285=1% vs 14/176=8%; $p<0.0001$). Furthermore, cases of *P. vivax* infection were diagnosed in patients who had returned from India (5 cases), French Guyana (1 case), Kenya (1 case). Cases of *P. ovale* infection were diagnosed in patients who had returned from Cameroon (4 cases), Ivory Coast (3 cases), Burkina Faso (1 case) and Indonesia (1 case).

Food-borne and water-borne infections were the second most common cause of fever in our patients with 23 cases of gastrointestinal tract infection including gastroenteritis (9 cases), typhoid fever due to culture-proven *Salmonella typhi* (5 cases), shigellosis due to culture-proven *Shigella flexneri* or *S. sonnei* (4 cases), dysentery (3 cases), non-typhoidal salmonellosis (*S. enteritica*, 1 case), and amoebiasis (1 case). Typhoid fever was diagnosed in patients who had returned from Algeria (1 case), Mali (1 case), India (2 cases) and Peru (1 case). Shigellosis was diagnosed in patients who had returned from Africa including Gabon (1 case), Niger (1 case) and Senegal (1 case), and India (1 case). Hepatitis A and E infections were diagnosed in patients returning from Mali and China, respectively.

Respiratory tract infections were the third most frequent cause of fever identified in our patients with 21 cases. One case of Legionnaire diseases was diagnosed in a patient returning from Ivory coast (by serology and urine antigen), and 2 cases of *Mycoplasma pneumoniae* infections (in patients returning from Comoros and French Guyana, respectively). Eleven of the patients were hospitalized in 2003 during the SARS epidemic. They had

returned from Southeastern Asia and were hospitalized to exclude the diagnosis of SARS.

Dengue fever virus was the second most common pathogen identified after *Plasmodium* spp. A total of 13 cases were documented. Six patients acquired the disease in Asia including in Cambodia (3 cases), India (2 cases) and Lao (1 case); 3 patients in Africa (Cameroon, Senegal and Somalia, respectively); 2 patients in the West Indies; and 1 in Brazil. There were no diagnoses of dengue hemorrhagic fever or shock syndrome. All cases were confirmed by serology. Febrile patients who returned from Asia were significantly more likely to present with dengue than patients who had returned from other places (OR, 13.4; 95% CI, 3.7-48.1; $p<0.0001$).

Other diagnoses included 1-3 cases of the following (Table 1): hepatitis B, hepatitis C, amoebic liver abscess, loiasis due to *Loa loa*, lymphatic filariasis due to *Wuchereria bancrofti* and *Brugia malawi*, schistosomiasis due to *Schistosoma haematobium*, strongyloidiasis, gnathostomiasis, EBV infection, CMV infection, leprosy, ecthyma; rickettsiosis (Indian tick typhus due to *Rickettsia conorii indica* and African tick bite fever due to *Rickettsia africae*), Q fever, toxoplasmosis, pyelonephritis, viral syndrome, Reiter syndrome, eosinophilia, and chronic diarrhea. Two cases of HIV infection in migrants were diagnosed. A total of 51 cases (8.2%) were identified as febrile illness with no confirmed diagnosis.

Discussion

The evaluation of fever in the returned traveler requires an understanding of the common etiologies encountered by the population of travelers, which may include local specificities.² To our knowledge, we present here the largest prospective study of patients who were hospitalized in one site for the assessment of febrile illness acquired overseas. Indeed, the data of 613 patients consecutively admitted over a period of 5 years were recorded in a specific medical record (called 'travel medical record') including a standard format. The only larger prospective study that we could find through a medline research was a 4-year prospective study conducted at the emergency department of a French hospital, and included 783 inpatient and outpatient adults.⁶ In our study, criteria of admission to our unit were not predefined. They were based on the judgement of the physician on duty, those who saw the returned patients at the emergency rooms, and infectious diseases physicians seeing the patients who first presented at the tropical diseases outpatients clinic before being

Table 1 Primary discharge diagnoses in 613 patients hospitalised in Marseille, southern France, after returning from tropical areas, 1999-2003.

Diagnosis	Number (%) of patients		
	Total	Comorians	Other
Malaria (<i>Plasmodium</i> species)	461 (75.2)	286 (88.3)	175 (60.6)
<i>P. falciparum</i>	421 (68.7)	259 (79.9)	162 (56)
Uncomplicated	386	250	136
+ <i>P. vivax</i> uncomplicated	7	3	4
+ <i>P. ovale</i> uncomplicated	6	1	5
+ <i>P. malariae</i> uncomplicated	2	1	1
Severe	17	3	14
Hyperreactive malaria syndrome	3	1	2
<i>P. vivax</i>	24 (3.9)	17 (5.2)	7 (2.4)
<i>P. ovale</i>	14 (2.3)	9 (2.8)	5 (1.7)
<i>P. malariae</i>	1	1	0
<i>Plasmodium</i> sp.	1	0	1
Febrile illness, no confirmed diagnosis	50	24	26
Dengue	13	0	13
<i>Food born and water born infection</i>			
Gastroenteritis	9	2	7
Typhoid fever (<i>Salmonella typhi</i>)	5	0	5
Shigellosis (<i>Shigella flexneri</i> , <i>Shigella sonnei</i>)	4	0	4
Dysentery	3	0	3
Salmonellosis (<i>Salmonella enteritica</i>)	1	0	1
Intestinal amoebiasis (<i>Entamoeba histolytica</i>)	1	0	1
<i>Respiratory tract infection</i>			
Exclusion of SARS	11	0	11
Pneumonitis	4	2	2
<i>L. pneumophila</i>	1	0	1
<i>M. pneumoniae</i>	2	1	1
Other	1	1	0
Upper respiratory tract infection	3	1	2
Bronchitis	3	1	2
Strongyloidiasis (<i>Strongyloides stercoralis</i>)	2	1	1
<i>Viral hepatitis</i>			
Type A	1	0	1
Type B	1	1	0
Type C	3	2	1
Type B+Type C	1	1	0
Type E	1	0	1
Undetermined	1	0	1
Liver amoebiasis abscess	2	0	2
Loiasis	3	0	3
Lymphatic filariasis	3	1	2
<i>Wuchereria bancrofti</i>			
<i>Brugia malawi</i>			
<i>Schistosomiasis (S. haematobium)</i>			
Katayama fever	1	0	1
Urinary schistosomiasis with appendicitis	1	0	1
Mononucleosis (acute EBV infection)	2	0	2
Cytomegalovirus primo infection	1	0	1
Eosinophilia	2	0	2
Gnathostomiasis	1	0	1
Lymphangitis secondary to myiasis (<i>C. anthropophaga</i>)	1	0	1
Leprosy	1	1	0

(continued on next page)

Table 1 (continued)

Diagnosis	Number (%) of patients		
	Total	Comorians	Other
Ecthyma	1	1	0
Tickborne spotted fever group rickettsioses			
<i>Rickettsia africae</i>	1	0	1
<i>Rickettsia conorii</i>	1	0	1
Q fever (<i>Coxiella burnetii</i>)	2	1	1
HIV-AIDS	2	0	2
Associated with malaria	1	0	1
Associated with <i>Mycobacterium avium</i> complex infection, pyelonephritis and strongyloidiasis	1	0	1
Toxoplasmosis	1	0	1
Pyelonephritis (<i>E. coli</i> , <i>E. faecalis</i>)	2	1	1
Reiter's syndrome	1	0	1
Viral syndrome	1	1	0
Chronic diarrhea	5	0	5
Miscellaneous non-infective	4	1	3
Total	613	324	289

hospitalized. All of them have however, the instructions to admit systematically patients with falciparum malaria.

In our study, malaria was the cause of the fever in 75.2% of the 613 returned patients. Therefore, it was by far the most common cause of fever, as reported in other similar studies.^{3,6-10} *Plasmodium falciparum* was the most commonly identified species (91.3%), which mirrors the national French records,¹¹ and more generally the European records.¹² The risk to travelers of acquiring malaria is known to vary according to the destination.¹³ Most of our cases were acquired in Comoros Islands (62%) and sub-Saharan Africa (31.5%). Furthermore, febrile patients who returned from the Comoros archipelago or the African mainland were significantly more likely to present with malaria. This is attributed to the fact that the majority of our patients are migrants (59.4%), and that most of the migrants originated from Comoros Islands (84%), and less frequently Western Africa (9%). Indeed, in recent years, a growing proportion of imported malaria has been seen in migrants, both in Europe and America.¹³ These migrants include newcomers and refugees, but even more frequently residents who return to their countries of origin to visit friends and relatives (VFR). In a recent review of reports describing more than 250 cases and published between 1991 and 2001, the proportion of migrants in malaria cases in Europe varied from 33% in the United Kingdom to 60% in Italy and 86% in France¹⁴. Interestingly, this last study was conducted in our hospital, in the paediatrics unit.¹⁵

On pooling the reports, 43% of the cases registered in major European centre occurred in migrants and VFRs make up the dominant group.¹⁴

The Comoros archipelago includes four Islands located in the Indian Ocean covering 2300 km² with a population of some 726,000 inhabitants. Three islands form the Comoros Union (formerly Federal Islamic Republic of the Comoros), independent since 1975, whereas Mayotte Island has remained a French territory. In spite of malaria control programs, falciparum malaria still constitutes a major public health problem in the Comoros Union.¹⁶ There have been two waves of immigration from Comoros to France. The first started before 1970 and the second followed the independence of the three islands after 1975. In Marseilles, the population of people originating from Comoros has been estimated at 50,000-70,000 inhabitants, although the precise number is difficult to assess. Further, it has been estimated that 4000-5000 people originating from Comoros and living in France are traveling back to Comoros every year, primarily to visit friends and relatives.¹⁷

Based on self reports available for 304 (94%) of 324 patients who had returned from the Comoros Archipelago, most of them did not use a chemoprophylaxis regimen or took inadequate regimens. Only one patient (0.33%) took an adequate regimen (mefloquine) regularly during and after the trip as currently recommended by the French health authorities¹⁸. However, drug levels were not measured to confirm the claim of this patient. The poor compliance to malaria chemoprophylaxis in

migrants returning to their country of origin to visit friends and relatives corroborates with other reports in the literature^{13,14}. The reasons for poor compliance include the lack of information, as well as the misconception in continued immunity against malaria because of birth in Comoros, and the relatively high cost of the drugs recommended for chemoprophylaxis. As discussed recently, an improved approach to educate the Comorian population in Marseilles regarding malaria risks and prophylaxis needs to be explored and include the contribution of social and medical anthropology¹⁷.

Following *Plasmodium* spp., dengue fever virus was the second most common identified pathogen responsible of fever in our travelers, with 13 cases. Dengue fever represented 2.1% of the diagnoses among our febrile patients, 19% of those returning from South-America and West Indies, and 20% of those who had returned from Southeastern Asia. Dengue virus was also identified as the second most frequent cause of fever in returned travelers in two recent studies conducted in Australia⁸ and in Italy³. Interestingly, 3 of our dengue cases (23%) were acquired during a trip to sub-Saharan Africa. In recently reported reviews of dengue cases diagnosed in Europe, 10.3-21% of cases came from Africa^{19,20}. Dengue fever is now recognized as a global pandemic with recorded prevalence in 101 countries in Central and South America, Asia, Pacific, Australia, and Africa²¹. Interestingly, one of our patient had dengue fever associated with shigellosis²².

Dengue as a traveler's disease has been recently reviewed²¹. Among the studies analyzed in this review, one had been performed prospectively among 104 young long-term travelers (at least 3 months) from Israel to various endemic areas²³. Dengue seroconversion was reported in 6.7% of all travelers with a median of 5.3 months' stay abroad; four travelers (3.8%) had immunoglobulin (Ig) M antibodies, all after a trip to Southeast Asia; three out of seven infection were asymptomatic²³. Another prospective study conducted in a cohort of Dutch short-term travellers to endemic areas in Asia during 1991-92 included collection of sera before and after travel²⁴. The authors reported an incidence rate of probable infection (IgM seroconversion or a fourfold rise in IgG ratio in the absence of cross-reaction with antibody to Japanese encephalitis virus) of 30/1000 persons/months, with a clinical/subclinical ratio of 1:3.3²⁴. Higher incidence rates have been reported during epidemics. In August 1995, a dengue virus outbreak among participants in a community-assistance program in Tortola, British Virgin Islands, Caribbean, resulted

in an attack rate was reaching 69%²⁵. Non-Caucasian travellers may have a higher risk for developing dengue hemorrhagic fever than Caucasian travellers²¹. Finally, the role of travelers to introduce more virulent strains (subtypes) into areas where only mild disease had been observed (such as Sri Lanka), or to introduce the virus to non-endemic areas where the mosquito vector *Aedes aegypti* is prevalent, has been recently discussed²¹.

Foodborne and water-borne infections made up the second most common group of infections diagnosed in our febrile travelers. This is not surprising as gastrointestinal illnesses, particularly diarrhea, are the most commonly reported disorders in travelers². Gastroenteritis was the second leading cause of fever in most of the studies recently reviewed³. In febrile patients, gastrointestinal symptoms can be caused by bacteria responsible for invasion of the mucosal lining of the intestines, including *Salmonella* spp. and *Shigella* spp., as observed in our patients. Fever is uncommon in *E. histolytica* infections, with the exception of hepatic amebiasis, as reported here. Of significance is the fact that *S. typhi*, the causative agent of typhoid fever, is the leading etiologic agent responsible for food- and water-borne infections in our patients. None of the patients had been given typhoid vaccine. Antinori et al. noted a similar trend³. Typhoid fever is diagnosed with an incidence rate of 30/100,000 per month among travelers to the Indian subcontinent, North and West Africa (except Tunisia) and Peru. Elsewhere this rate has been estimated to be 10-fold lower²⁶. Tourists as well as VFRs are affected²⁶. In France, the health authorities recommend it for long-term stays or for trips in countries with a low level of hygiene and sanitation, especially for back-packers or foreign-aid-volunteers during trips in small villages and rural areas off the usual tourist routes¹⁸.

The cases of hepatitis A and hepatitis E in our study may be included in the discussion of food- and water-borne infections. The patient who acquired hepatitis A was a 25-year-old traveler who was born and resided in France. Because of improved hygiene and housing conditions over the past 20 years, France has become a country with low endemicity for hepatitis A. As a consequence, there is an increased proportion of adults susceptible to the virus. For example, a serosurvey was performed in 1997 in 1052 French army recruits (mean age: 21.2 years)²⁷. Overall anti-hepatitis A virus seroprevalence was 11.5%. The greatest risk factor of hepatitis A infection was related to travel in medium or highly endemic areas: 46% of overseas residents (odds ratio=10.3), 28% of recruits who had travelled in developing countries (odds ratio=3.7) and 7.65% of

French living in industrialized countries were hepatitis A seropositive²⁷.

The French sentinel network of general practitioners enables the continuous monitoring of hepatitis A incidence in metropolitan France²⁸. From 1991 to 1996, 415 cases of acute hepatitis A were reported and travel was the primary risk factor (25%)²⁸. Hepatitis A is the most frequent vaccine-preventable infection in non-immune travelers to developing countries with an average incidence rate of 300/100,000 per month, up to 2000/100,000 in back-packers and foreign-aid volunteers²⁶. Children born to migrants living in France and travelling back to the family's country of origin are particularly vulnerable. The Asian and African region bordering the Mediterranean and the Caribbean have been classified as destinations with moderate to high risk of infection by WHO²⁶. Currently, the efficacy of hepatitis A vaccination is close to 100%²⁹. In France, the vaccine is now recommended in unimmunized adults and children over the age of one year traveling to endemic areas, and more generally for all travelers to all countries with poor sanitation level. Serologic testing prior to vaccination is recommended only for persons born before 1945, for those residing in medium-high endemic areas, and those with a medical history of jaundice¹⁸. In Switzerland, the 'universal travel strategy' for hepatitis A vaccination was associated with a 9-year reduction rate of 54%²⁹.

Hepatitis E virus (HEV) is known since the 1990s as a major cause of clinical hepatitis in the endemic regions, including Asia, Africa, Central and South America, the Middle East, and the Republics of the former USSR³⁰. It is usually transmitted via the fecal-oral route, and contaminated drinking water. However, HEV rarely causes disease in more industrialized countries, where most of the cases are related to travel. In 1999, Schwartz et al. found 148 reported travel related hepatitis E cases in the literature over the period 1986-1997³¹, including one case in a patient returned from China, such as our patient. Although the incidence of HEV infection in travelers seems to be low, compared with hepatitis A infection, a more consistent diagnostic approach may lead to increased diagnoses in the future^{31,32}.

In our study, respiratory tract infections were the third most frequent cause of fever with 21 cases. Half of these patients were hospitalized in 2003 after returning from Southeast Asia to exclude the diagnosis of severe acute respiratory syndrome (SARS)³³. The SARS outbreak has recently focused global attention on respiratory tract infection in returned travellers³⁴. In early 2003, the Geosentinel Surveillance Network published a review of

respiratory tract infections in travellers recorded in their database by 25 globally dispersed sentinel clinics from September 1997 through August 2001. Among 21,960 entries, respiratory tract infections accounted for 7.8% of all infections and included various respiratory diagnosis³⁵. These data highlighted the susceptibility of travelers to infectious respiratory pathogens even before the SARS epidemic. Possible respiratory problems included viral upper respiratory tract infection, bronchitis, viral and bacteria pneumonia, followed by uncommon or more 'exotic' causes². More recently, the medical records of travelers who had returned with pneumonia and who had been hospitalized in Paris in a French Hospital from August 2001 to July 2002, were reviewed³⁶. A total of 17 patients were studied. The authors reported a high rate of etiologic diagnosis (76.5%), that they explain by their inclusion criteria, 'severe disease or unexplained cause'³⁶. They reported *L. pneumophila* and *M. pneumoniae*, as reported in our study³. They also diagnosed *Streptococcus pneumoniae*, *Leptospira* sp., *Mycobacterium tuberculosis*, *Histoplasma capsulatum* and *Schistosoma* sp. as well as agents that were in our study responsible for syndromes other than respiratory infections, such as *Coxiella burnetii*, the agent of Q fever, and dengue virus³⁶. Although Legionnaire's disease is now recognized as a relatively common cause of pneumonia in travelers, particularly after sea cruises³⁷, most of the causes of respiratory tract infections in travelers are not identified, particularly when patients are not hospitalized. A systematic procedure for laboratory investigation is on going for all patients admitted in our unit. The benefit of such a procedure to diagnose respiratory tract infections will be evaluated in the upcoming months.

In our patients, two cases of acute pyelonephritis were diagnosed. A prior report found upper urinary tract infections to be the second leading cause of fever after malaria, in 67 women returning from the tropics to Paris, France³⁸. As stated by the authors, urinary infections are favoured by hot climates, lack of hydration as well as poor hygienic conditions, and should be systematically sought in women with fever after returning from abroad³⁸.

Among other infections diagnosed, 2 cases of HIV infection were identified in 2 migrants. The first was a woman who had arrived from Ethiopia. She was hospitalized for malaria. Her HIV status was not known when she arrived and we proposed an HIV test because of recent weight of loss. The second case was a Cambodian woman who returned to France with her French boyfriend. Her HIV status was known for 6 months, and her medical history included pneumocystis pneumonia. Her final

diagnoses in our unit included HIV/AIDs with *Mycobacterium avium* complex infection, pyelonephritis and oesophageal candidiasis. Thus, HIV testing should be considered in migrants recently arrived from countries of high endemicity, even if a common diagnosis such as malaria has been identified. No case of HIV infection in travelers were reported in our study, although this has been described in an other paper⁸. Other viral infections, EBV infection and CMV infections, have also been identified in our study. Both infections are seldom reported in febrile patients after a trip overseas^{3,8}.

Finally, other causes of fever in our study include several emerging infectious diseases, such as gnathostomiasis. This disease is acquired by eating uncooked food infected with the larval third stage of *Gnathostoma* spp. helminth; such foods typically include fish, shrimp, crab, crayfish, frog, or chicken³⁹. The disease is well known in endemic areas of southeastern Asia, Japan, and South-America and has been increasingly reported in travelers in recent years³⁹⁻⁴¹. Our last case presented not as a typical cutaneous form but as eosinophilic pleural effusion with fever in a patient who had returned from Vietnam⁴².

Rickettsial diseases, including emerging pathogens, can affect the travelers as demonstrated in our study. These diseases may include tick-borne spotted fever group rickettsioses, murine typhus, epidemic typhus, scrub typhus and Q fever. Although *C. burnetii*, the agent of Q fever has been removed from the *Rickettsiales*, Q fever is often still considered in the differential of rickettsial diseases. In the past, we have reported a case imported from Senegal⁴³. In the present study, one case occurred in a traveller who had returned from French Guyana, South America. A second case was associated with falciparum malaria in a patient returning from Comoros. It should be remembered that Q fever may present with isolated fever⁴⁴. Furthermore, a recent review found 400 cases of tick-borne spotted fever group rickettsioses in international travellers, the vast majority being African tick bite fever caused by *R. africae* and Mediterranean spotted fever caused by *R. conorii*⁴⁵. The present study reported only two cases because most of our patients with tick-borne rickettsioses are seen as outpatients; however, these cases were sufficiently severe to require hospitalisation. One case was reported as the first serologically documented case of Indian tick typhus in a returned traveler⁴⁶. Our study did not detect any flea-borne murine typhus due to *R. typhi*, or scrub typhus due to *Orientia tsutsugamushi* transmitted by chiggers, although these diseases are

potential causes of fever in returned travelers^{47,48}. Finally, the louse-borne epidemic typhus due to *R. prowazekii* can also present as fever in migrants from countries where they were living in poor conditions, as we reported in the past⁴⁹. All these reports should encourage travelers to use personal protective measures against arthropod bites^{45,50}.

In conclusion, this study is one of the largest conducted in febrile travelers hospitalised after returning from overseas. Malaria was shown to be by far the most frequent cause of fever. Migrants who visited friends and relatives in their country of origin appeared to be at high risk, as shown in other recent studies. Our study highlights the need to adapt travel advices and chemoprophylaxis to the community of migrants. In our city, it includes a large proportion of people originated from the Comoros archipelago. Thus, our data may not be representative for other centers in Europe or anywhere. However, these centers may face similar situation with others specific communities of migrants. Finally, although we have identified here emerging diseases, 8.2% of the fevers remained unexplained. An improved approach to diagnosis may allow for the discovery of new diseases in travelers in the future.

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