Etiology and Outcome of Fever After a Stay in the Tropics

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Background: Information on epidemiology and prognosis of imported fever is scarce and almost exclusively limited to hospital settings.

Methods: From 2000 to 2005, all travelers presenting at our referral outpatient and inpatient centers with ongoing fever within 12 months after a stay in the tropics were prospectively followed. Case definitions and treatment were based on international recommendations. Outcome was assessed by at least 1 follow-up consultation or telephone call within 3 months after initial contact.

Results: A total of 1842 fever episodes were included, involving 1743 patients. Regions of exposure were mainly sub-Saharan Africa (68%) and the Southeast Asia-Pacific region (12%). Tropical diseases accounted for 39% of all cases and cosmopolitan infections for 34%. Diagnosis often remained unknown (24%). The pattern of tropical diseases was mainly influenced by the travel destination, with malaria (35%, mainly *Plasmodium falciparum*) and rickettsial infection (4%) as the leading diagnoses after a stay in Africa; dengue (12%), malaria (9%), and enteric fever (4%) after travel to Asia; and dengue (8%) and malaria (4%) on return from Latin America. Disease pattern varied also according to the category of travelers, the delay between exposure and fever onset, and the setting. Hospitalization was required for 503 fever episodes (27%). *Plasmodium falciparum* malaria accounted for 36% of all admissions and was the only tropical cause of death (5 of 9 patients). Fever of unknown cause had invariably a favorable outcome.

Conclusion: The clinical spectrum of imported fever is highly destination specific but also depends on other factors. *Plasmodium falciparum* malaria was the leading cause of mortality in the study population.

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INTERNATIONAL TRAVEL HAS increased tremendously in the last decades.[1] Consequently, Western physicians are increasingly confronted with sick travelers or migrants potentially exposed to various exotic infections. Roughly 10% of travelers to developing countries experience a febrile illness during travel or on return.[2-4] Fever is a leading reason for posttravel consultation, together with diarrhea and skin disorders.[5-7] It is also a challenging clinical problem, particularly for physicians unfamiliar with imported pathologic conditions, because of the wide differential diagnosis, the nonspecific features of most tropical diseases, and the risk of severe causative infections.[8-10]

Recently, the global epidemiology of travel-related illnesses has been updated.[5] However, specific information on the clinical spectrum and prognosis of imported fever is rather limited and almost exclusively hospital based.[11-16] Our study was aimed at investigating the etiology and outcome of fever after a stay in the tropics and assessing the specific burden of tropical pathologic conditions.

METHODS

STUDY DESIGN AND SETTING

The study was conducted at the Institute of Tropical Medicine (ITMA) and at the University Hospital Antwerp (UHA) in Antwerp, Belgium. The ITMA is the national reference center for tropical medicine and provides pretravel and posttravel outpatient care as well as chronic care for patients with AIDS. The UHA is a tertiary care referral hospital, where the ITMA physicians supervise the inpatient Department of Tropical Diseases and emergency posttravel consultations when the ITMA travel clinic is closed (nights and weekends). The Belgian health system allows patients to present to referral structures on their own.

From April 2000 to March 2005, all febrile patients of any age seen at the above centers were included in this prospective study on the condition that a tropical or subtropical country was visited within the previous 12 months.

DEFINITIONS

The following 4 categories of travelers were defined: Western travelers (natives of Western countries visiting the tropics for less than 6 months); expatriates (Western individuals residing for more than 6 months in the tropics); natives of the tropics who have lived for more than 1 year in Europe and returning to their home country to visit friends and relatives (VFR travelers); and foreign visitors or migrants (natives of the tropics arriving for the first time in Europe). Fever was defined by a documented axillary temperature of 38°C or higher, or by the combination of febrile sensation, chills/rigor, and sweats within 3 days prior to consultation. Tropics and subtropics corresponded to all nonindustrialized countries at least partly situated between the 35°-northern and 35°-southern latitude.

DIAGNOSTIC PROCEDURE

Clinical data were collected during consultation using electronic case-record forms. All patients were offered the following laboratory examinations: total blood cell count with differential, liver, and kidney function tests; thick and thin blood smears if travel to malaria-endemic regions; urinalysis; and blood cultures at febrile peaks. Other investigations were ordered according to the clinician's decision.

Etiologic diagnosis was made according to internationally recognized case definitions.[17,18] It was confirmed if a pathogenic microorganism was demonstrated in a relevant specimen or if a seroconversion to an infectious agent was documented. Strict case definitions combining clinical findings and single serologic testing results were used to identify highly probable etiologic diagnoses. Final diagnosis could be clinical if fever was undisputedly due to a specific syndrome (such as erysipelas or orchitis). In case of concomitant infections, the most severe febrile disease defined the final diagnosis. Febrile episodes not fulfilling any precise etiologic or clinical diagnosis were of "unknown cause"; in these cases a presumptive diagnosis was reported.

TREATMENT, FOLLOW-UP, AND OUTCOME

Patients were treated according to international guidelines. All patients were followed prospectively until clinical cure could be assessed by at least 1 follow-up consultation or telephone call. Disease was considered as chronic if cure was not complete after 3 months. If no contact was established within 3 months after the initial consultation, the patient was considered lost to follow-up.

STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS software, version 13 (SPSS Inc, Chicago, Ill). The χ^2 test was used to compare categorical variables; parametric and nonparametric tests were used when appropriate for continuous variables. All tests were 2-tailed, and $P<.05$ indicated statistical significance.

ETHICS ISSUES

All patients or their legal representatives were informed about the study objectives and case management. The diagnostic workup was performed in a reasonable way and without excessive costs. Patient data were rendered anonymous for further analyses according to the Belgian legislation. The study was designed, conducted, and analyzed independently of any sponsoring. The protocol was approved by the ethics committee of the ITMA.

RESULTS

STUDY POPULATION CHARACTERISTICS

During the 5-year period, 1842 febrile episodes occurred in 1743 patients. In nearly 6% of all cases, the patient had to interrupt his or her travel or be repatriated. Most cases were presented first at the travel clinic of the ITMA (n=1469; 80%) and the remaining at the emergency ward (UHA). As shown in **Table 1**, the majority of patients were Western travelers (60%), whereas expatriates (14%), VFR travelers (14%), and foreign visitors or migrants (12%) were fewer in number but similar in importance. The mean age was 36 years (range, 0.5-82 years) but was younger in foreign visitors or migrants ($P<.001$).

Sub-Saharan Africa was by far the most frequent region of exposure (68%). It had been visited by 55% of the Western travelers and by nearly 90% of the patients belonging to the other 3 categories. The Southeast Asia-Pacific region was the second most popular travel destination (12%). Only a small subset of travelers (pilots, sailors, and stewards: 2%) had visited more than 1 region within 1 month before consulting, but a substantial amount did so when travel during the past 1 year was taken into account (n=276; 15%).

Malaria chemoprophylaxis was completely taken by only 33% of Western travelers and even much less so by expatriates (10%) and VFR travelers (19%) ($P<.001$). When restricting to the subgroup returning from sub-Saharan Africa, prophylaxis was adequate (mefloquine, atovaquone-proguanil, or doxycycline) in 199 (33%) of 596 Western travelers, in 10 (4%) of 238 expatriates, and in 30 (14%) of 217 VFR travelers.

Western travelers were more likely to have previously consulted a general practitioner (36%). Many patients, in particular expatriates (42%), had already taken an empirical treatment, often on their own initiative.

Of note, about 10% of all patients presented with an important underlying condition, including 6% with human immunodeficiency virus (HIV)/AIDS and nearly 1% with pregnancy.

SYMPTOMS AND SIGNS AT PRESENTATION

In 78% of all cases, fever occurred during travel or within 1 month of return or arrival. Median fever duration before consulting us was 4 days. Temperature was documented (≥38°C) by the patient and/or the physician in 87% of all fever episodes.

Digestive and respiratory symptoms were frequent (Table 1). Fever was reported as the only symptom by nearly 20% of the patients. Findings from physical examination were unremarkable in more than 50% of the cases. Clinical features were similar in all 4 traveler categories, except that skin disorders and enlarged lymph nodes were more frequent in Western travelers and that respiratory symptoms and enlarged spleen predominated in foreign visitors or migrants ($P<.001$ for each feature).

Table 1. Epidemiological and Clinical Characteristics of the Study Population per Category of Travelers*

Variable	Western Travelers (n = 1098)	Expatriates (n = 266)	VFR Travelers (n = 249)	Foreign Visitors or Migrants (n = 229)	Total (N = 1842)
Patient characteristics					
Sex, male	690 (63)	171 (64)	157 (63)	129 (56)	**1147** (62)
Age, mean ± SD, y	37.5 ± 14	38.5 ± 17.5	35 ± 11	29 ± 15	36 ± 14.5
Children, age <15 y	33 (3)	29 (11)	15 (6)	40 (17)	**117** (6)
Elderly, age ≥60 y	80 (7)	31 (12)	2 (1)	6 (3)	**119** (6)
Last visited region/continent					
Africa	655 (60)	240 (90)	222 (89)	204 (89)	**1321** (72)
Sub-Saharan Africa	596 (54)	238 (89)	217 (87)	203 (89)	**1254** (68)
North Africa	59 (5)	2 (1)	5 (2)	1 (0.4)	**67** (4)
Asia	299 (27)	22 (8)	20 (8)	14 (6)	**355** (19)
Southeast Asia-Pacific region	198 (18)	16 (6)	11 (4)	5 (2)	**230** (12)
Indian subcontinent	84 (8)	4 (2)	9 (4)	6 (3)	**103** (6)
Middle East	17 (2)	2 (1)	0	3 (1)	**22** (1)
Latin America	108 (10)	4 (2)	6 (2)	11 (5)	**129** (7)
Central America/Caribbean	57 (5)	2 (1)	3 (1)	4 (2)	**66** (4)
South America	51 (5)	2 (1)	3 (1)	7 (3)	**63** (3)
>1 Region	36 (3)	0	1 (0.4)	0	**37** (2)
Prophylaxis/reference pattern/previous treatment, No. (%)					
Complete malaria prophylaxis	363 (33)	26 (10)	47 (19)	0	**436** (24)
Previous contact with other physician	397 (36)	52 (20)	66 (27)	55 (24)	**570** (31)
Transfer from other hospital	44 (4)	8 (3)	13 (5)	13 (6)	**78** (4)
Previous antibiotics and/or antimalarial treatment	350 (32)	113 (43)	74 (30)	51 (22)	**588** (32)
Time lapse from return or arrival to fever onset					
Before return or arrival	404 (37)	101 (38)	59 (24)	37 (16)	**601** (33)
0-3 mo	611 (56)	152 (57)	155 (62)	117 (51)	**1035** (56)
4-12 mo	82 (7)	13 (5)	34 (14)	75 (33)	**206** (11)
Clinical symptoms at presentation					
Fever duration, median (IQR), d	4 (2-7)	4 (2-7)	4 (3-7)	4 (3-7)	4 (2-7)
Headache and/or myalgia	804 (73)	201 (76)	200 (80)	167 (73)	**1372** (74)
Any digestive symptom†	609 (56)	160 (60)	123 (49)	126 (55)	**1018** (55)
Any pulmonary symptom‡	344 (31)	76 (29)	83 (33)	106 (46)	**609** (33)
Fever as the only symptom	193 (18)	44 (17)	52 (21)	40 (17)	**329** (18)
Clinical findings at presentation					
High-grade fever, temperature ≥39°C	456 (42)	131 (49)	93 (37)	83 (36)	**763** (41)
Skin rash/other skin lesions	194 (18)	25 (9)	16 (6)	19 (8)	**254** (14)
Enlarged lymph nodes	135 (12)	25 (9)	28 (11)	45 (20)	**233** (13)
Enlarged spleen	84 (8)	37 (14)	22 (9)	48 (21)	**191** (10)
Abnormal upper respiratory tract examination§	78 (7)	15 (6)	21 (8)	29 (13)	**143** (8)
Abnormal lung auscultation	47 (4)	15 (6)	17 (7)	29 (13)	**108** (6)
Temperature ≥38°C as the only sign	593 (54)	147 (55)	141 (57)	84 (37)	**965** (52)

Abbreviations: IQR, interquartile range; VFR, visiting friends and relatives.
*Data are given as number (percentage) unless otherwise specified.
†Including vomiting, and/or diarrhea, and/or abdominal pain.
‡Including cough, and/or dyspnea, and/or chest pain.
§Including clinical pharyngitis, and/or tonsillitis, and/or otitis, and/or sinusitis.

DIAGNOSIS OF IMPORTED FEVER

A definitive diagnosis, etiologic or clinical, was established in 1393 fever cases (76%) (**Table 2**). Standard diagnostic tests were not complete in 35 episodes (2%). Of all patients, 10% had more than 1 infection and some even had several plausible causes of fever (4%). Tropical infections accounted for 39% of all causes of fever, with malaria by far the most prominent cause. Rickettsial infection, dengue, acute schistosomiasis, enteric fever, and invasive amebiasis were considerably less frequent. Diagnosis was confirmed in 80% of the cases of rickettsial infection, 75% of dengue, 82% of acute schistosomiasis, and in almost all other tropical diseases.

Cosmopolitan infections were frequent as well (34%). Diagnosis was etiologic in 411 (65%) of 631 cases and confirmed in 85% of them, and it was clinical in the remaining 220 episodes (35%). Respiratory tract infection, bacterial enteritis, mononucleosis-like syndrome, skin/soft tissue infection, and genitourinary infection were the leading causes. Hepatitis A was notably rare. Diagnosis of HIV infection was established during the fever workup in 26 of the 116 patients with this condition.

The cause of fever remained unknown in 24% of patients. Most of these episodes were probably due to self-limiting intestinal and upper respiratory tract infections. In contrast, fever heralded a noninfectious disease in only 2%.

When comparing diseases per traveler category (**Table 3**), *Plasmodium falciparum* malaria was more frequently diagnosed in expatriates, VFR travelers, and foreign visitors or migrants ($P<.001$), whereas rickettsial infection, dengue, and acute schistosomiasis occurred almost exclusively in Western travelers and expatriates. Prevalence of HIV infection and tuberculosis was dramatically higher in VRF travelers and foreign visitors or migrants. By contrast, referral had little impact on disease etiology, except for rickettsial infection that was more often seen previously by another practitioner (6% vs 2%; $P<.001$).

The pattern of tropical disease depended greatly on the travel destination (**Figure**). Respiratory tract infection, bacterial enteritis, and fever of unknown cause were equally frequent in patients returning from the 3 main tropical continents. In contrast, *Plasmodium falciparum*, *Plasmodium malariae*, and *Plasmodium ovale* malaria, rickettsial infection, and acute schistosomiasis were almost exclusively diagnosed in patients arriving from Africa. *Plasmodium vivax* malaria, dengue, and enteric fever were the leading tropical causes of fever after a stay in Asia. Tropical infections were infrequent in travelers returning from Latin America and almost exclusively due to dengue and *Plasmodium vivax* malaria. Of note, the actual place of infection was uncertain for 23 patients with nonfalciparum malaria who had visited more than 1 region in the previous year.

Finally, disease pattern varied according to the time lapse between exposure and onset of fever. Indeed, most tropical infections became symptomatic before or within 1 month of return or arrival (595/722 [82%]), including all dengue and rickettsial infections (**Table 4**). Malaria was the largely predominant cause of the tropical infections that developed during the second or third month since return (66/79 [84%]) and the almost exclusive cause of the few tropical fevers emerging later (44/48 [92%]).

DIAGNOSTIC PROCEDURE

Definitive diagnosis was made by blood smear examination in 513 episodes (28%), by clinical examination in 250 (17%), by paired serologic testing in 189 (10%), by stool examination and/or culture in 131 (7%), by single serologic testing in 112 (6%), by urinalysis and/or urine culture in 65 (4%), by chest radiography in 53 (3%), and by blood culture in 30 (2%). The other investigations required for the 50 remaining definitive diagnoses included mainly sputum culture, abdominal ultrasonography, and lumbar puncture.

EVOLUTION AND OUTCOME

Complete follow-up data were obtained for 98% of the patients. In total, 503 (27%) were hospitalized, including 431 (23%) immediately and 72 (4%) later in the course of the disease. Patients who attended the emergency ward were admitted much more often compared with those seen at the travel clinic (292/373 [78%] vs 211/1469 [14%]); they were also more often referred (44% vs 33%) and presented more frequently with serious symptoms such as high-grade fever (temperature ≥39°C) (52% vs 39%) or vomiting (31% vs 15%).

Table 2. Diagnosis of Imported Fever

Condition	Cases, No. (%) (N = 1842)
Tropical diseases	722 (39.2)
Plasmodium falciparum malaria	408 (22.1)
Nonfalciparum malaria	103 (5.6)
Plasmodium vivax	50 (2.7)
Plasmodium ovale	38 (2.1)
Plasmodium malariae	15 (0.8)
Rickettsial infections	60 (3.3)
Rickettsia conori/africae (African tick bite fever/Mediterranean spotted fever)	53 (2.9)
Rickettsia typhi (murine typhus)	4 (0.2)
Orienta tsutsugamushi (scrub typhus)	3 (0.2)
Dengue fever	56 (3.0)
Acute schistosomiasis (Katayama fever)	33 (1.8)
Enteric fever	15 (0.8)
Salmonella typhi	8 (0.4)
Salmonella paratyphi A	7 (0.4)
Invasive amebiasis	10 (0.5)
Protozoan enteritis*	10 (0.5)
Other tropical diseases†	27 (1.5)
Cosmopolitan infections	631 (34.2)
Respiratory tract infection‡	194 (10.5)
Bacterial enteritis§	115 (6.2)
Infectious mononucleosis-like syndromes‖	72 (3.9)
Skin/soft tissue infection	67 (3.6)
Genitourinary infection¶	63 (3.4)
Tuberculosis	30 (1.6)
Bacteremia#	18 (0.1)
Q fever	13 (0.7)
Hepatitis A	11 (0.6)
AIDS-related opportunistic infections (other than tuberculosis)	10 (0.5)
Leptospirosis	6 (0.3)
Other infections (≤5 cases for each diagnosis)	32 (1.7)
Unknown causes	449 (24.4)
No focus of infection	168 (9.1)
Symptoms of enteritis	151 (8.2)
Symptoms of upper respiratory tract infection	130 (7.1)
Noninfectious causes	40 (2.2)

*Including *Cyclospora* species (n = 7), *Isospora belli* (n = 2), and *Cryptosporidium* species (n = 1).

†Including histoplasmosis (n = 5), Löffler syndrome (n = 4), helminthic enteritis (n = 4), human African trypanosomiasis (n = 3), hepatitis E (n = 3), *Shigella dysenteriae* enteritis (n = 3), sarcocystosis (n = 3), relapsing fever (n = 1), and angiostrongyloidiasis (n = 1).

‡Including pharyngitis, and/or tonsillitis, and/or otitis, and/or sinusitis (n = 59); pneumonia diagnosed by chest radiographs (n = 52); bronchitis diagnosed clinically (n = 42); *Chlamydia* or *Mycoplasma pneumoniae* infection (n = 25); and influenza A or B (n = 16).

§Including *Shigella* species (n = 33), *Campylobacter* species (n = 30), *Salmonella* species (n = 18), *Yersinia* species (n = 3), and presence of white and/or red blood cells in stool examination without isolation of pathogenic bacteria (n = 31).

‖Including primary infection with cytomegalovirus (n = 35), *Toxoplasma gondii* (n = 16), Epstein-Barr virus (n = 15), and human immunodeficiency virus (n = 5).

¶Including 15 diagnoses of sexually transmitted disease (secondary syphilis, n = 4; *Chlamydia trachomatis*, n = 4; genital herpes, n = 4; and *Mycoplasma genitalis*, n = 3).

#Including bacteremia due to *Escherichia coli* (n = 8), *Salmonella* species other than *Salmonella typhi* or *Salmonella paratyphi* (n = 3), *Streptococcus pneumoniae* (n = 3), *Neisseria meningitidis* (n = 2), *Listeria monocytogenes* (n = 1), and *Streptococcus pyogenes* (n = 1).

Hospitalized patients were slightly older, more often referred, and less likely to be Western travelers or expatriates (**Table 5**). Tropical infections, most being *Plas-*

Table 3. Prevalence of the Main Diagnoses According to Category of Travelers*

Main Diagnosis	Western Travelers (n = 1098)	Expatriates (n = 266)	VFR Travelers (n = 249)	Foreign Visitors or Migrants (n = 229)
Plasmodium falciparum malaria	159 (14)	100 (38)	90 (36)	59 (26)
Nonfalciparum malaria	59 (5)	19 (7)	7 (3)	18 (8)
Rickettsial infection	57 (5)	3 (1)	0	0
Dengue	48 (4)	5 (2)	3 (1)	0
Acute schistosomiasis	30 (3)	2 (1)	1 (0.4)	0
Enteric fever	11 (1)	1 (0.4)	2 (1)	1 (0.4)
Invasive amebiasis	5 (0.5)	3 (1)	0	2 (1)
Respiratory tract infection	104 (9)	22 (8)	27 (11)	41 (18)
Bacterial enteritis	87 (8)	14 (5)	7 (3)	7 (3)
Tuberculosis	2 (0.2)	0	7 (3)	21 (9)
Unknown cause	302 (28)	50 (19)	66 (27)	31 (14)
HIV infection, No./No. tested (%)	22/372 (6)	8/136 (6)	32/131 (24)	54/134 (40)

Abbreviations: HIV, human immunodeficiency virus; VFR, visiting friends or relatives.
*Data are given as number (percentage) of cases (N = 1842).

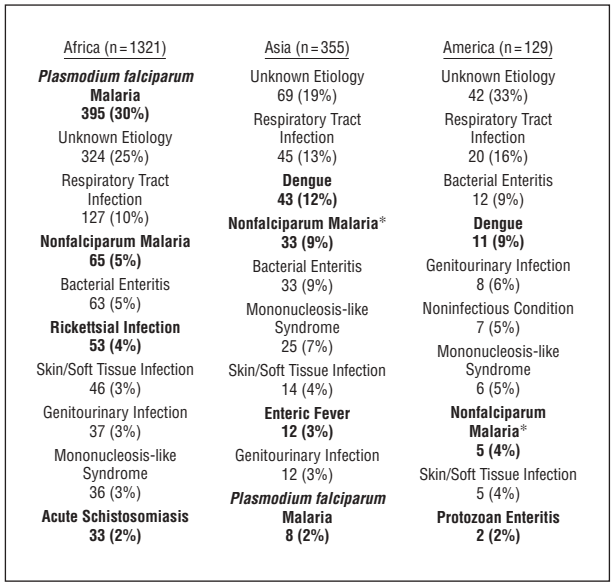

Figure. Ranked prevalence of imported febrile diseases (tropical cause in boldface) according to last continent of exposure: top 10 diagnoses. Thirty-seven other patients had visited more than 1 continent, including 5 diagnosed as having *Plasmodium falciparum* malaria and 1 as having rickettsial infection. *Exclusively *Plasmodium vivax* malaria.

modium falciparum malaria, accounted for nearly 50% of all admissions (Table 5). Thirty-nine patients were admitted in the intensive care unit, and 9 died (2% and 0.5% of all fever cases, respectively). *Plasmodium falciparum* malaria was the only tropical disease leading to admission to the intensive care unit (n = 30) and to death (n = 5; fatality rate of 1.2%). The median hospital duration was 4 days (interquartile range, 2-7 days).

The hospitalization rate was high for invasive amebiasis (60%), enteric fever (47%), and *Plasmodium falciparum* malaria (44%); intermediary for dengue (21%) and nonfalciparum malaria (18%); and low for acute schistosomiasis (9%) and rickettsial infection (8%). In 91% of the fever episodes, patients were completely cured within 3 months. Another 8% had been diagnosed as having a chronic disease (mainly HIV infection or tuberculosis). None of the surviving patients with malaria developed long-term sequels. All patients with fever of unknown cause recovered uneventfully except for one who relapsed and was later diagnosed as having peritoneal tuberculosis. These febrile patients were less often hospitalized (10% vs 33%), were more often treated symptomatically (72% vs 29%), and had a shorter fever duration (4 vs 7 days) compared with those with a definite diagnosis ($P<.001$ for all 3 comparisons).

COMMENT

To date, imported fever has been almost exclusively studied in hospitalized patients. This prospective study provides additional information by including a large sample of ambulatory patients as well and by investigating the outcome. Moreover, data collection, first-line workup, and treatment protocols were standardized, reducing uncertainties inherent to its observational design. However, limitations are to be mentioned. First, case definitions were strict when paired serum samples were not available, and investigations were not irrationally extensive for mild self-limiting illnesses. As a consequence, the prevalence reported herein should be viewed as minimal figures, with probably few erroneous positive diagnoses but an undetermined number of missed diagnoses in the fevers of unknown cause.[19] Second, a certain selection bias was unavoidable in our referral centers. However, the important nonreferred population reflected to a certain extent patients seen at a primary care level. As the prevalence of the main tropical diseases was similar among referred and nonreferred patients, the selection bias was probably limited. The fact that rickettsial infection was more frequently seen in referred patients suggests that it was not correctly recognized by general practitioners.[20]

The physical findings associated with imported fever are most of the time unremarkable and rarely provide a diagnostic clue. Moreover, presentation may be altered in patients presenting with mixed infections and/or comorbidity. Therefore, complementary investigations are essential for a sound diagnosis or for limiting the diagnostic spectrum.[8,9,12]

Table 4. Prevalence of Tropical Diseases According to Period Between Return or Arrival From Endemic Countries and Fever Onset*

Tropical Disease	Before and Within the First Month of Return or Arrival (n = 1434)	Within the Second Month of Return or Arrival (n = 137)	Within the Third Month of Return or Arrival (n = 66)	Within 4-12 Months of Return or Arrival (n = 205)	Total, No. (N = 1842)
Plasmodium falciparum malaria	373 (26)	20 (15)	7 (11)	8 (4)	**408**
Nonfalciparum malaria	28 (2)	23 (17)	16 (24)	36 (18)	**103**
Rickettsial infection	60 (4)	0	0	0	**60**
Dengue	56 (4)	0	0	0	**56**
Acute schistosomiasis	24 (2)	6 (4)	2 (3)	1 (0.5)	**33**
Enteric fever	14 (1)	1 (1)	0	0	**15**
Invasive amebiasis	7 (0.5)	1 (1)	0	2 (1)	**10**
Protozoan enteritis	9 (1)	0	1 (2)	0	**10**
Other tropical diseases	24 (2)	2 (1)	0	1 (0.5)	**27**
Total tropical diseases	**595** (41)	**53** (39)	**26** (39)	**48** (23)	**722**

*Data are given as number (percentage) of cases unless otherwise specified. Percentages may not add to total owing to rounding.

Because sub-Saharan Africa was the predominant travel destination in this as in other European studies,[11-13] its disease pattern shifts heavily toward malaria and skews all other diagnoses to a lesser importance.[5] However, this study is large enough to provide robust data on imported fever from other continents as well. It illustrates clearly that the pretest probability of malaria is far greater after a stay in Africa (35%) than after a journey to Asia (10%) or to Latin America (<5%). As expected from its epidemiology, dengue is more likely to occur in a febrile traveler returning from any of the latter 2 destinations.[16,21] Likewise, enteric fever is more prevalent in travelers to Asia,[22] and acute schistosomiasis as well as African tick bite fever is exclusively linked to travel to Africa.[23,24] As such, this study contributes to a quantification of the geographic risk for the main tropical diseases and confirms that travel destination is a key element in the diagnostic approach of imported fever.[5]

Cosmopolitan infections and unknown causes of fever are also very frequent.[13,15,25] Comparisons with other published series are difficult because data were often lacking and case definitions were not standardized. Strikingly, hepatitis A appears to be much less frequent here than in the largest historical series,[15] probably as a result of pretravel vaccination. However, a recent Italian study did not confirm this declining trend.[11] Tuberculosis is not rare in this series but is almost exclusively diagnosed in natives of highly endemic countries. Sexually transmitted diseases and HIV infection, including the acute retroviral syndrome, should also be systematically considered in febrile travelers or migrants for their evident public health implications.[26]

The time lapse between exposure and onset of symptoms is another key element for diagnosis. When fever strikes within 3 months of return or arrival, and particularly within the first month, expertise of travel physicians may be helpful to physicians unfamiliar with exotic pathologic conditions because numerous tropical infections must be considered.[8] In contrast, malaria is the almost exclusive tropical infection that may still emerge in the late posttravel period. Therefore, blood smear microscopy is the only investigation required in a basic workup to rule out a tropical condition in a febrile patient with a remote travel history.

Table 5. Clinical and Diagnostic Data of Hospitalized and Ambulatory Patients*

Variable	Hospitalized Patients (n = 503)	Ambulatory Patients (n = 1339)	*P* Value
Clinical characteristics			
Age, mean ± SD, y	38.5 ± 15.0	35.5 ± 14.5	<.001
Children, age <15 y	15 (3)	102 (8)	<.001
Elderly, age ≥60 y	50 (10)	69 (5)	<.001
Western traveler or expatriate	338 (67)	1006 (75)	.001
Previous contact with other physician	232 (46)	416 (31)	<.001
Previous antibiotic and/or antimalarial treatment	183 (36)	405 (30)	.01
Fever duration before contact, median (IQR), d	4 (3-7)	4 (2-7)	.40
Prevalence of tropical disease			
Plasmodium falciparum malaria	180 (36)	228 (17)	<.001
Nonfalciparum malaria	19 (4)	84 (6)	.04
Rickettsial infection	5 (1)	55 (4)	<.001
Dengue	12 (2)	44 (3)	.30
Acute schistosomiasis	3 (1)	30 (2)	.02
Enteric fever	7 (1)	8 (1)	.09
Invasive amebiasis	6 (1)	4 (0.3)	.02
Protozoan enteritis	0	10 (1)	.07
Other tropical diseases	10 (2)	17 (1)	.20
Total tropical diseases	**242** (48)	**480** (36)	<.001

Abbreviation: IQR, interquartile range.
*Data are given as number (percentage) of cases (N = 1842) unless otherwise specified.

Disease pattern also varies according to the category of travelers. The VFR travelers represent a well-identified risk group because of specific behavior and exposure.[27] Morbidity profile is indeed different for this demographic group, but it is also different for expatriates, who do not present the same risks and attitudes as the short-term travelers. Not surprisingly, the predominance of ambulatory patients corrects somehow the underestimation of milder tropical infections classically observed in hospital-based series.[11,13,16] The setting-specific impact on malaria prevalence is less clear because admission policy varies largely between European countries.

A limited laboratory workup sufficed to establish diagnosis early and reliably in half of the patients (mostly malaria cases). Sophisticated diagnostic procedures were rarely needed. However, many tropical diseases such as arboviruses and rickettsioses require repeated serological testing for confirmation, causing considerable delay and underestimation of their true prevalence. Therefore, efforts should be maintained to improve direct pathogen detection during the febrile phase.[24,28]

Despite the high mobility of the population, the outcome of imported tropical illnesses has been properly evaluated in this study. Here again, *Plasmodium falciparum* malaria accounted for all the severe morbidity (intensive care unit admissions) and mortality associated with tropical diseases.[29,30] Indeed, no other tropical disease appeared to be fatal when correctly managed. However, morbidity (hospital admissions) was notable, despite the fact that most cases were assessed by experienced clinicians. But this study also clearly indicates that when no specific cause was established after a reasonable workup, fever after travel invariably resulted from a mild and self-limiting condition with a favorable prognosis.

In conclusion, diagnostic assessment of imported fever should rely mainly on geographic exposure, but it should also rely on specific risk profiles and clinical parameters. Prognosis is dramatically affected by the burden of *Plasmodium falciparum* malaria. Differential diagnosis is particularly critical when fever develops within 3 months of return or arrival because it includes infections with the highest morbidity and mortality risk. Early diagnosis of the main tropical conditions would further improve patient management.

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