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Original Article

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Causes of fever in returning travelers: a European multicenter prospective cohort study

Daniel Camprubí-Ferrer, MD[1], Ludovico Cobuccio, MD[2,3], Steven Van Den Broucke, MD[4], Blaise Genton, PhD[2,3], Emmanuel Bottieau, PhD[4], Valérie d'Acremont, PhD[2,3], Natalia Rodriguez-Valero, MD[1], Alex Almuedo-Riera, MD[1], Leire Balerdi-Sarasola, MD[1], Carme Subirà, BSc[1], Marc Fernandez-Pardos, BSc[1], Miguel J. Martinez, PhD[5], Jessica Navero-Castillejos, MD[5], Isabel Vera, BSc[1], Jara Llenas-Garcia, PhD[6,7], Camilla Rothe, PhD[8], Dániel Cadar, PhD[9], Marjan Van Esbroeck, MD[4], Nikki Foque, MD[4], and Jose Muñoz, PhD[1]

[1]ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain, [2]Swiss Tropical and Public Health Institute, Basel, Switzerland, [3]Center for Primary Care and Public Health, University of Lausanne, Switzerland, [4]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium, [5]Microbiology Department, Hospital Clínic Barcelona, Spain, [6] Internal Medicine – Infectious Diseases, Vega Baja Hospital, Orihuela, Alicante, Spain, [7]Clinical Medicine Department, University Miguel Hernández, Elche, Alicante, Spain, [8]Division of Infectious Diseases and Tropical Medicine, University Hospital LMU, Munich, Germany and [9]Bernhard Nocht Institute for Tropical Medicine, National Reference Centre for Tropical Pathogens, Hamburg, Germany

*To whom correspondence should be addressed. Email: dcamprub@clinic.cat; Tel:+34 93 227 18 52

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Abstract

Background: Etiological diagnosis of febrile illnesses in returning travelers is a great challenge, particularly when presenting with no focal symptoms [acute undifferentiated febrile illnesses (AUFI)], but is crucial to guide clinical decisions and public health policies. In this study, we describe the frequencies and predictors of the main causes of fever in travelers.

Methods: Prospective European multicenter cohort study of febrile international travelers (November 2017–November 2019). A predefined diagnostic algorithm was used ensuring a systematic evaluation of all participants. After ruling out malaria, PCRs and serologies for dengue, chikungunya and Zika viruses were performed in all patients presenting with AUFI $\leq$ 14 days after return. Clinical suspicion guided further microbiological investigations.

Results: Among 765 enrolled participants, 310/765 (40.5%) had a clear source of infection (mainly traveler's diarrhea or respiratory infections), and 455/765 (59.5%) were categorized as AUFI. AUFI presented longer duration of fever ($p < 0.001$), higher hospitalization ($p < 0.001$) and ICU admission rates ($p < 0.001$). Among travelers with AUFI, 132/455 (29.0%) had viral infections, including 108 arboviruses, 96/455 (21.1%) malaria and 82/455 (18.0%) bacterial infections. The majority of arboviral cases (80/108, 74.1%) was diagnosed between May and November. Dengue was the most frequent arbovirosis (92/108, 85.2%). After 1 month of follow-up, 136/455 (29.9%) patients with AUFI remained undiagnosed using standard diagnostic methods. No relevant differences in laboratory presentation were observed between undiagnosed and bacterial AUFI.

Conclusions: Over 40% of returning travelers with AUFI were diagnosed with malaria or dengue, infections that can be easily diagnosed by rapid diagnostic tests. Arboviruses were the most common cause of AUFI (above malaria) and most cases were diagnosed during *Aedes* spp. high season. This is particularly relevant for those areas at risk

of introduction of these pathogens. Empirical antibiotic regimens including doxycycline or azithromycin should be considered in patients with AUFI, after ruling out malaria and arboviruses.

Key words: Diagnosis, predictor, febrile, travel-related illness, arboviruses, malaria, doxycycline

Introduction

Acute febrile illnesses are the leading cause of consultation to an emergency room, hospitalization and death among returning travelers.[1] There are many causes of imported fever in returning travelers, making its etiological diagnosis a great challenge, especially when presenting with no focal symptoms, thus being considered acute undifferentiated febrile illnesses (AUFI).

Plasmodium falciparum malaria has consistently been reported as the leading cause of travel-related fever.[2–5] However, its decreasing incidence in most endemic areas in the last years as well as the emergence of other microorganisms forces to reassess the current main etiologies of fever in returning travelers and migrants.[6] In addition, in most series approximately between one-sixth and one-third of patients remain undiagnosed even at referral centres.[3,7,8] There are numerous narrative reviews on causes of fever in returning travelers but only one systematic review and meta-analysis.[2] Most studies consist of monocentric/country-specific case series with high heterogeneity in laboratory investigations.[2,7,8]

Causes of imported fever have traditionally been divided into tropical and non-tropical diseases.[2,3,5] However, factors such as international human mobility, climate change, the emergence of new pathogens and the description of autochthonous cases of some tropical diseases in European countries are blurring this categorization.[6] Therefore, physicians in non-tropical countries should be prepared to recognize and treat the main febrile illnesses classically related to travel. The diagnosis of these diseases depends not only on a high degree of clinical suspicion but also on specific diagnostic tests that are seldom available in non-specialized settings. Moreover, clear guidance on empirical antibiotic treatment for imported fever is lacking. The use of beta-lactams in these cases is widespread, but the role of antibiotics active against intracellular bacteria is uncertain. Therefore, identification of the current etiologies of imported fever is crucial not only to improve the management, including the necessity (or not) of empirical antibiotic treatment, but also to recognize pathogens at high risk of introduction into Europe.[9–11]

In this study, we describe the frequencies and diagnostic predictors of the main causes of AUFI in a prospective European cohort of travelers and recently arrived migrants.

Methods

Study design

This is a prospective multicenter cohort study of international returning travelers or recently arrived migrants with fever attending three European Travel Clinics and/or Hospitals from November 2017 to November 2019: Hospital Clinic of Barcelona/Barcelona Institute for Global Health, Spain; Institute of Tropical Medicine, Antwerp, Belgium and University Centre for Primary Care and Public Health, Lausanne, Switzerland.

Adult travelers (age $\geq$ 18 years) presenting with axillary temperature $\geq$ 37.5°C (or feverish sensation and at least two of the following symptoms: sweats, chills/shivering or myalgia) in the previous 72 h, returning from an international travel within the previous 28 days were eligible to participate.

Study workflow and laboratory procedures

In all recruited participants, demographics, previous medical conditions, travel history and exposures, as well as symptoms, physical examination and laboratory data were collected using a study-specific case report form. Diagnostic procedures were performed at each study site following a predefined clinical algorithm (Supplementary Figure 1). Follow-up visits took place 3, 7 and 28 days after enrolment.

Participants were classified at day of inclusion as patients with focal symptoms [traveler's diarrhea (TD), defined as >3 stools/day; respiratory tract infections; urinary tract infections; or skin and soft tissue infections] or patients with AUFI. A blood smear was performed in all patients returning from malaria endemic areas. Once malaria was ruled out, targeted polymerase chain reaction (PCR) tests and paired specific antibody tests against dengue, chikungunya and Zika viruses were performed in all patients presenting with AUFI onset during travel or $\leq$ 14 days after return. Serologies and targeted PCRs against *Leptospira* spp. and *Rickettsia* spp., blood cultures, human immunodeficiency virus (HIV) test as well as other microbiological tests were performed according to the clinician's suspicion. Final diagnosis was classified as microbiologically confirmed or probable (Supplementary Table 1). Participants with $\geq$1 diagnosis were allowed to classify in different diagnostic categories.

Complicated imported fever was defined as the presence of $\geq$1 of the following conditions: > 7 days of fever after initial consultation; decreased level of consciousness or seizures; systolic blood pressure $\leq$ 100 mmHg; C-reactive protein (CRP) > 10 mg/dL; alanine transaminase (ALT), aspartate transaminase (AST) or gamma-glutamyl transpeptidase (GGT) > 400 IU/L; bilirubin > 3 mg/dL; creatinine > 1.3 mg/dL; lactate dehydrogenase (LDH) > 1000 IU/L; platelets $<50 \times 10^9$/L.

Data management and statistical analysis

The statistical analysis was performed using Stata15 (Stata Corp LLC, College Station, TX). Regarding the bivariate analysis, numeric parameters were compared using *t*-test or ANOVA. Mann–Whitney U test or Kruskal–Wallis tests were used for variables with non-normal distribution. Categorical variables were compared between groups using the Pearson χ^2 test or Fisher's exact test. To identify factors associated with the different causes of AUFI, all significant variables from the bivariate analysis were included in a multivariate logistic regression model,

allowing estimating adjusted odds ratios (aORs) for variables identified through backward stepwise selection. Positive and negative likelihood ratios (LRs+, LRs−) were also calculated.[12]

Ethics

The study was designed in compliance with Good Clinical Practice and following the Declaration of Helsinki. This study was approved by local IRB and Ethics Committees in all study sites. Written informed consent was obtained from all study participants.

Results

Study population and baseline characteristics

In total, 765 patients fulfilling the eligibility criteria were included from November 2017 to November 2019 in the three recruiting sites: 491/765 (64.2%) in Barcelona (Spain), 185/765 (24.2%) in Lausanne (Switzerland) and 89/765 (11.6%) in Antwerp (Belgium). About 406/765 (53.1%) were male with a median age of 36 years (IQR: 28–47); 211/765 (27.6%) patients had previous medical conditions and 39/765 (5.1%) had an immunosuppressive condition (Table 1).

Regarding the main visited World Health Organization (WHO) regions, 331/765 (43.3%) patients visited Africa, 180/765 (23.5%) South-East Asia (SEA), 159/765 (20.8%) the Americas and 110/765 (14.4%) West Pacific. The main reasons of travel were tourism (438/765, 57.3%) and visiting friends and relatives (VFRs) (133/765, 17.4%). Median travel duration was 17 days (IQR: 13–29), being shorter for business travelers (11.5 days) and longer for VFR (29 days) and volunteers (34.5 days) ($p < 0.001$). About 634/765 (82.9%) patients visited rural areas and 676/765 (90.3%) recognized at least one travel-associated risk exposure; 442/765 (60.2%) returning travelers with fever had not attended a pretravel consultation. Among patients travelling to malaria high-endemic areas, 125/290 (43.1%) took antimalarial chemoprophylaxis, but 47/125 (37.6%) of them did not take it properly (Table 1).

Clinical presentation

Patients presented with a median duration of symptoms of 4 days (IQR: 2–8) and a median duration of fever of 3 days (IQR: 2–6). VFRs presented with longer duration of fever (4 days, IQR: 2–8, $p < 0.001$). Overall, most common focal symptoms were: diarrhea in 308/765 (40.3%), cough in 268/765 (35.0%) and rhinorrhea in 162/765 (21.2%). By contrary, most common general symptoms were: headache in 534/765 (69.8%), fatigue in 631/765 (82.5%) and myalgia in 423/765 (55.3%). Retro-orbital pain occurred in 274/765 (35.8%) febrile travelers. Physical examination revealed generalized rash, hepatomegaly, jaundice and splenomegaly in 166/765 (21.7%), 34/765 (4.4%), 29/765 (3.8%) and 13/765 (1.7%) travelers presenting with fever, respectively. An eschar was detected in 20/765 (2.6%) febrile patients (Supplementary Table 2). Table 2 shows hematology and biochemistry results in patients with AUFI.

Etiologies

Although 227/765 (29.7%) initially presented with focal symptoms and 538/765 (70.3%) with AUFI, at the end of the follow-up, 310/765 (40.5%) were finally diagnosed with a clear source of infection (SoI), 415/765 (54.2%) with an AUFI and 40/765 (5.2%) with mixed infections (coinfections of SoI and AUFI) (Supplementary Figure 2). Diagnostic confirmation was achieved in 442/765 (57.8%) patients, with no differences between patients with SoI and AUFI ($p = 0.362$). Table 3 and Supplementary Figure 3 show the final diagnosis of patients with imported fever.

SoI. About 350/765 (47.8%) patients finally presented at least one SoI: 155/350 (44.3%) presented with respiratory infections and 165/350 (47.1%) with TD. Microbiological confirmation of patients with a SoI was obtained in 212/350 (60.6%) (Table 3). Nasopharyngeal swabs allowed diagnosing 82/107 (76.6%) of respiratory cases in which they were performed (Supplementary Table 3). 17/155 (11.0%) respiratory infections were caused by bacteria: *Streptococcus* spp. ($n = 10$), *Haemophilus influenzae* ($n = 2$), *Escherichia coli* ($n = 2$), *Staphylococcus aureus* ($n = 1$), *Mycoplasma pneumoniae* ($n = 1$) and *Bordetella pertussis* ($n = 1$). Supplementary Tables 4 and 5 show the detailed microbiological diagnosis of patients with TD and the Enterobacteriaceae antimicrobial resistance patterns.

AUFI. Approximately 445/765 (58.2%) patients were finally diagnosed with AUFI or mixed infections. Causes of AUFI were: (i) malaria (96/455, 21.1%); (ii) viral infections (132/455, 29.0%); (iii) bacterial infections (82/455, 18.0%); (iv) other infections (15/455, 3.3%) and (v) non-infectious diseases (15/455, 3.3%). After 1 month of follow-up, 136/455 (29.9%) patients with AUFI remained undiagnosed.

P. falciparum accounted for 85/96 (88.5%) of malaria cases; seven patients presented with non-falciparum malaria (4 *Plasmodium ovale*, 2 *Plasmodium vivax* and 1 *Plasmodium malariae*) and four were diagnosed with mixed *Plasmodium* infections. All malaria cases were microbiologically confirmed. Malaria was diagnosed by blood smear in 87/96 (90.6%) cases. The remaining nine patients who presented with a negative blood smear had received an antimalarial drug before the blood smear was performed and were diagnosed by rapid diagnostic tests (RDTs) and/or PCR. Antigen tests resulted positive in 53/57 (93.0%) malaria cases and 2/3 (66.7%) of non-falciparum malaria cases. *Plasmodium* PCR allowed the diagnosis of species in 31/34 (91.2%) of malaria cases tested.

Among viral infections, arboviruses were the main etiology, accounting for 108/455 (23.7%) cases with AUFI; 92/108 (85.2%) patients with arboviral infections were diagnosed with dengue fever, 9/108 (8.3%) with Chikungunya, 6/108 (5.6%) with Zika virus, 1 with West-Nile virus and 1 with tick-borne encephalitis. Microbiological confirmation was achieved in 87/108 (80.6%) arboviral cases. Acute HIV infection was diagnosed in 5/455 (1.1%) patients with AUFI. Other viral infections were cytomegalovirus ($n = 7$), Epstein–Barr virus ($n = 2$), hepatitis A virus ($n = 2$) and hantavirus ($n = 1$), amongst other.

Table 1. Patients' baseline characteristics, trip and exposure to travel-associated risk factors

	N = 765
Patients' baseline characteristics	
Female sex, *n* (%)	359 (46.9)
Age, Md (IQR)	36 (28–47)
European origin, *n* (%)	604 (79.0)
Type of traveler, *n* (%)	
– Tourist	438 (57.3)
– Visiting friends and relatives	133 (17.4)
– Expatriate/volunteer	90 (11.8)
– Business/studies	90 (11.8)
– Migrant/refugee	10 (1.3)
Recruitment place, *n* (%)	
– Outpatient	442 (57.8)
– Emergency department	270 (35.3)
– Inpatient	53 (6.9)
Previous medical conditions, *n* (%)	
Any previous medical conditions	211 (27.6)
– Immunosuppression*	39 (5.1)
– Cardiovascular risk factors	60 (7.8)
– Cardiovascular disease	23 (3.0)
– Respiratory condition	25 (3.3)
– Gastroenterological/hepatic disease	35 (4.6)
– Rheumatological/autoimmune condition	18 (2.4)
– Psychiatric/mental disease	15 (2.0)
– Other medical conditions	61 (8.0)
Chronic treatment, *n* (%)	156 (20.4)
Previous imported infections, *n* (%)	
– Previous malaria	93 (12.8)
– Previous dengue	17 (2.3)
Trip characteristics and travel-associated risk factors	
WHO region, *n* (%)	
– Africa	331 (43.3)
– South-East Asia	180 (23.5)
– Americas	159 (20.8)
– West Pacific	110 (14.4)
– East Mediterranean	30 (3.9)
– Europe	15 (2.0)
> 1 WHO region	54 (7.1)
Number of countries visited, *n* (%)	
1	640 (83.7)
2–3	102 (13.3)
≥ 4	23 (3.0)
Travel duration, Md (IQR)	17 (13–29)
Visited area, *n* (%)	
– Urban	131 (17.1)
– Rural	113 (14.8)
– Both	521 (68.1)
Risk factors, *n* (%)	
Any risk factor	676 (90.3)
– Long return trip (≥8 h in the same vehicle)	353 (48.6)
– Drinking non-bottled water	345 (46.7)
– Contact with fresh water	278 (36.9)
– Close contact with animals	236 (31.8)
– Eating raw fish, snails or crustaceans	108 (14.5)
– Unprotected sexual relationship	100 (13.7)
– Cave visit	64 (8.8)
– Parenteral transmission risk	43 (5.8)
– Unpasteurized dairy products	47 (6.3)
– Tick bite	36 (4.9)

(Continued)

Table 1. Continued

	N = 765
– Eating raw meat	30 (4.0)
– Contact with body fluids of a person	28 (3.8)
– Professional contact with patients	17 (2.3)
– Lice bite	14 (1.9)
– Contact with a potential tuberculosis case	12 (1.6)
Pretravel, vaccination and antimalarial prophylaxis	
Vaccination, *n* (%)	
–Yellow fever	387 (56.3)
–Typhoid	371 (56.0)
–Meningitis ACYW	98 (15.8)
–Influenza	48 (7.5)
–Japanese encephalitis	21 (3.2)
–Pneumococcal	18 (2.9)
–Tick-borne encephalitis	8 (1.2)
Pretravel advice, *n* (%)	292 (39.8)

*Immunosuppression: HIV (17), pharmacological (10), malignancy (10), transplant (3), asplenia (3), primary immunodeficiency (1).

Table 2. Comparative analysis of laboratory parameters among undiagnosed fevers and other causes of acute undifferentiated febrile illness (AUFI) of known origin

		Undiagnosed AUFI (*N* = 136)	Malaria (*N* = 96)		Virus (*N* = 132)		Bacterial AUFI (*N* = 82)	
	Normal range	Md (IQR)	Md (IQR)	*p-value*	Md (IQR)	*p-value*	Md (IQR)	*p-value*
Hemoglobin	130–170 g/dL	142 (130–149)	132 (118–145)	<0.001	143 (134–154)	0.102	141 (131–149)	0.821
Platelets	130–400 $\times 10^9$/L	217 (186–266)	98 (57–158)	<0.001	150 (125–201)	<0.001	223 (172–270)	0.624
WBC	4.0–11.0 $\times 10^9$/L	6.6 (4.8–9.0)	4.9 (3.7–5.8)	<0.001	4.0 (2.8–5.7)	<0.001	6.4 (5.4–8.1)	0.849
Neutrophils	2.0–7.0 $\times 10^9$/L	4.2 (2.7–6.3)	3.2 (2.5–4.3)	0.004	2.2 (1.7–3.4)	<0.001	4.3 (3.3–5.9)	0.339
Lymphocytes	0.9–4.5 $\times 10^9$/L	1.4 (1.0–1.9)	0.9 (0.5–1.2)	<0.001	0.8 (0.6–1.3)	<0.001	1.4 (1.0–1.7)	0.380
Eosinophils	< 0.5 $\times 10^9$/L	0.1 (0.0–0.1)	0 (0.0–0.1)	<0.001	0 (0.0–0.1)	<0.001	0·1 (0.0–0.1)	0.796
CRP	< 1.0 mg/dL	2.5 (0.5–5.5)	9.1 (3.6–16.1)	<0.001	1.0 (0.4–2.2)	<0.001	3.5 (0.6–8.6)	0.058
Creatinine	0.3–1.3 mg/dL	0.8 (0.7–1.0)	1.0 (0.8–1.2)	<0.001	0.9 (0.7–1.0)	0.291	0.9 (0.7–1.0)	0.402
Bilirubin	< 1.2 mg/dL	0·5 (0·4–0·9)	1·4 (0·7–2·1)	<0.001	0.5 (0.4–0.6)	0.013	0.6 (0.4–0.8)	0.986
AST	5–40 IU/L	24 (20–35)	38 (28–71)	<0.001	36 (28–70)	<0.001	31 (21–54)	0.014
ALT	5–40 IU/L	23 (15–39)	35 (22–64)	<0.001	37 (21–73)	<0.001	30 (19–60)	0.027
GGT	5–40 IU/L	25 (15–44)	59 (31–138)	<0.001	30 (19–54)	0.075	25 (15–44)	0.950
Alkaline phosphatase	46–116 IU/L	68 (60–83)	74 (61–95)	0.066	63 (50–74)	0.019	67 (56–88)	0.861
LDH	< 234 IU/L	201 (175–278)	308 (230–457)	<0.001	230 (202–354)	0.003	194 (168–234)	0.274

ALT: Alanine transaminase; AST: Aspartate transaminase; CRP: C-reactive protein; GGT: Gamma-glutamyl transpeptidase; LDH: Lactate dehydrogenase; WBC: white blood cells. Laboratory parameters of patients with undiagnosed AUFI were compared with patients presenting with other causes of AUFI (malaria, viral and bacterial AUFI).

Bacterial infections were the third cause of AUFI. *Rickettsia* spp. infections were diagnosed in 46/455 (10.1%) travelers with AUFI using standard methods: 44/46 (95.7%) were diagnosed by serology and 2/46 (4.3%) by PCR. Leptospirosis was diagnosed in 21/455 (4.6%) patients: 18/21 (85.7%) by serology and 3/21 (14.3%) by PCR in blood. Enteric fever was diagnosed in 6/455 (1.3%) patients: 4 typhoid and 2 paratyphoid fevers, respectively. All enteric fever cases were diagnosed by blood culture. Fluoroquinolone-resistant strains were detected in 4/6 (66.7%) of *Salmonella typhi/paratyphi* infections (Supplementary table 5). Other bacterial infections were Q fever ($n = 6$), syphilis ($n = 5$), Lyme disease ($n = 3$) and melioidosis ($n = 1$), amongst other.

Fifteen patients presented with other infections such as acute schistosomiasis ($n = 7$), other helminthiasis ($n = 2$), histoplasmosis ($n = 3$) and mycobacterial infections ($n = 3$). Supplementary Table 6 details the microbiological results of patients with AUFI.

Fifteen patients were diagnosed with non-infectious diseases. Most common causes of non-infectious AUFI were: autoimmune and rheumatologic diseases ($n = 10$), neoplasms and hematological conditions ($n = 2$), post-artesunate delayed hemolysis and other drug-induced fevers ($n = 2$) and psychiatric conditions ($n = 1$) (Table 3).

Undiagnosed AUFI. At the end of the follow-up, 136/455 (29.9%) patients with AUFI remained undiagnosed. Interestingly, when comparing undiagnosed AUFI with bacterial AUFI, no statistically significant differences were observed in laboratory parameters, except for AST ($p = 0.014$) and

Table 3. Diagnosis of patients with imported fever

	Final diagnosis (confirmed + probable)	Confirmed diagnosis
Source of infection (SoI)	*N* = 350	212 (60.6)
• Traveler's diarrhea	165 (47.1)	95 (57.6)
• Respiratory tract infection	155 (44.3)	99 (63.9)
• Skin and soft tissue infection	24 (6.9)	15 (62.5)
• Urinary tract infection	20 (5.7)	15 (75.0)
Acute undifferentiated febrile illness (AUFI)	*N* = 455	269 (59.1)
• Malaria	96 (21.1)	96 (100.0)
• Viral infections	132 (29.0)	103 (78.0)
Arbovirus	108 (23.7)	87 (80.6)
Dengue virus	92 (20.2)	77 (83.7)
Chikungunya	9 (2.0)	7 (77.8)
Zika virus	6 (1.3)	2 (33.3)
West-Nile virus	1 (0.2)	1 (100.0)
Tick-borne encephalitis	1 (0.2)	1 (100.0)
Other viral infections	24 (5.3)	16 (66.7)
HIV	5 (1.1)	5 (100.0)
CMV	7 (1.5)	3 (42.9)
EBV	2 (0.4)	0
HAV	2 (0.4)	2 (100.0)
Hantavirus	1 (0.2)	1 (100.0)
Other viruses*	7 (1.5)	5 (71.4)
• Bacterial infections	82 (18.0)	43 (52.4)
Rickettsia	46 (10.1)	17 (37.0)
Leptospira	21 (4.6)	7 (33.3)
Enteric fever	6 (1.3)	6 (100.0)
Q fever	6 (1.3)	4 (66.7)
Syphilis	5 (1.1)	5 (100.0)
Other bacteria*[2]	7 (1.5)	4 (57.1)
• Other infections	15 (3.3)	12 (80.0)
Mycobacteria	3 (0.7)	3 (100.0)
Helminths	9 (2.0)	6 (77.8)
Acute schistosomiasis	7 (1.5)	4 (57.1)
Other helminths*[3]	2 (0.4)	2 (100.0)
Histoplasmosis	3 (0.7)	3 (100.0)
• Undiagnosed AUFI	136 (29.9)	–
• Non-infectious diseases*[4]	15 (3.3)	15 (100.0)

CMV: cytomegalovirus; EBV: Epstein–Barr virus; HAV: hepatitis A virus; HHV6: human herpesvirus 6; ; *n*: number of cases; *N*: total number of travelers (globally or in each group)
*Other viral infections: HHV6, varicella, parotiditis, measles, Enterovirus meningitis.
*[2] Other bacterial infections: melioidosis (1), *Bartonella* spp. (1), Lyme (3), *S. aureus* endocarditis (1), appendicitis (1).
*[3] Other helminths: *Ancylostoma duodenale* (Löffler's syndrome) (1), *Strongyloides stercolaris* (1).
*[4] Non-infectious diseases: (i) Auto-immune/rheumatologic diseases [Reiter's syndrome (2), Chron's disease (2), thyroiditis (2), ankylosing spondylitis (1), hemophagocytic syndrome (1), systemic lupus erythematosus (1), gout (1)]; (ii) neoplasms/hematologic diseases [lymphoma (1), myelodysplastic syndrome (1)]; (iii) post-artesunate delayed hemolysis/drug-induced fevers (2); and (iv) psychiatric disorders (1).
Participants with ≥1 diagnosis were allowed to classify in different diagnostic categories.

ALT ($p = 0.027$). By contrast, when undiagnosed AUFI were compared with viral infections, differences in white blood cell count, platelet count, CRP, AST, ALT, alkaline phosphatase and LDH were observed. Differences were even more evident when undiagnosed AUFI were compared with malaria cases (Table 2 and Supplementary Figure 4).

Geographical and time distribution

Distribution of cases of imported fever was not homogeneous along the year, presenting a peak in August and September, reflecting international travel movements (Figure 1). However, respiratory infections did not present a seasonal distribution. Figure 2 and Supplementary Table 7 show the distribution of febrile travelers by WHO regions.

Overall, 93/96 (96.9%) malaria cases came from Africa and only 3 cases had visited other WHO regions such as Eastern Mediterranean ($n = 2$) or the Americas ($n = 1$). Among dengue cases, 37/92 (40.2%) came from SEA, 25/92 (27.2%) from the Americas, 23/92 (25.0%) from Western Pacific and 7/92 (7.6%) from Africa ($P < 0.001$). Chikungunya cases came from all WHO regions except Europe, Africa was the most common region of acquisition of chikungunya (3/9, 33.3%) and Zika viruses (3/6, 50.0%); 94/104 (87.0%) patients diagnosed with arboviral infections presented fever ≤5 days after return. Regarding the temporal distribution, 78/106 (73.6%) of arboviruses transmitted by *Aedes* spp. mosquitoes were diagnosed between May and November, coinciding with the highest *Aedes albopictus* activity in Southern Europe (Figure 1).

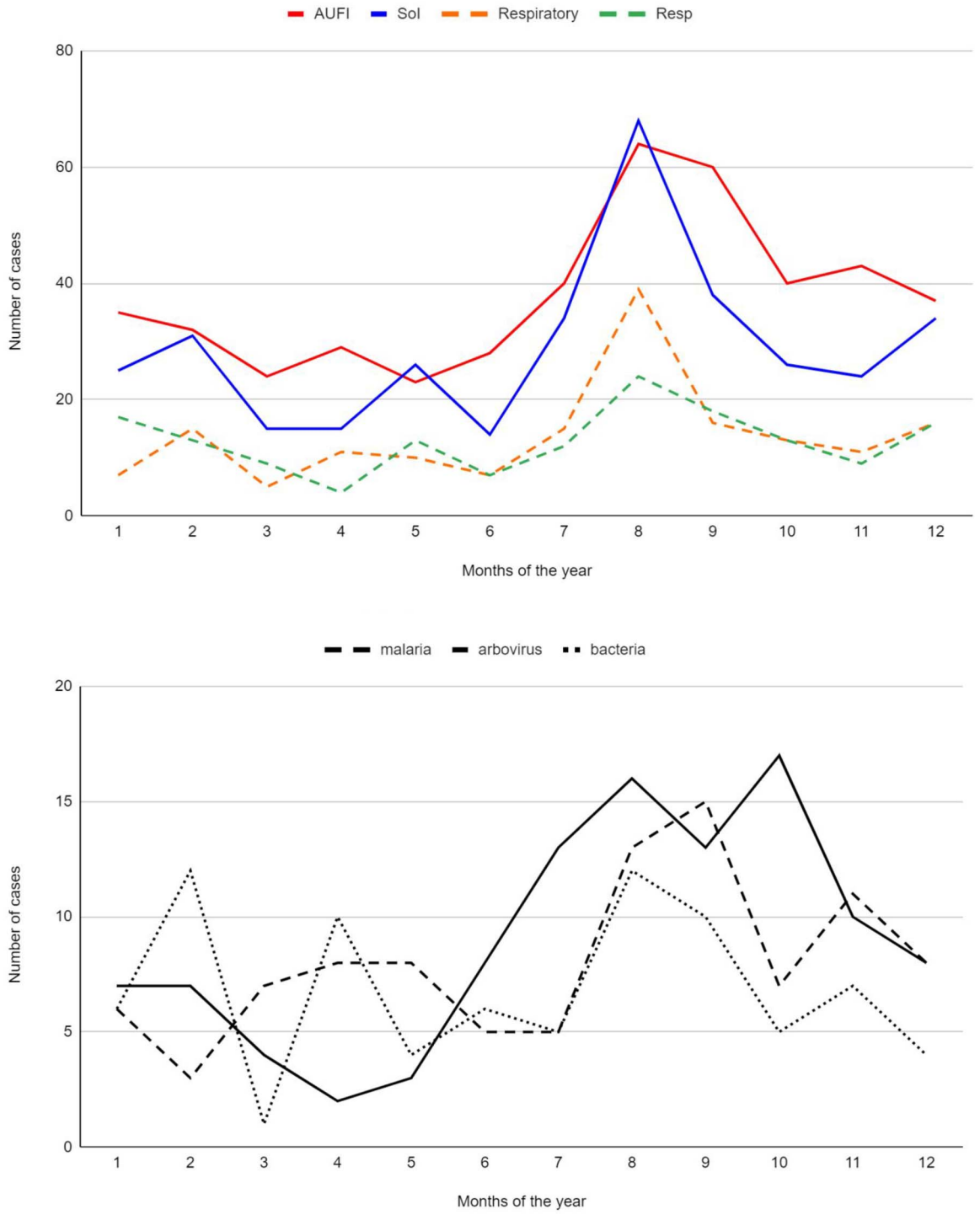

Figure 1. Temporal distribution of patients with imported fever. The first graph shows the temporal distribution of cases of AUFI (blue), SoI (red) as well as TD (dashed orange) and respiratory infections (dashed green) along the year (represented in months). The second graph shows the temporal distribution of cases of malaria (dashed black), arboviruses (black line) and bacterial AUFI (black points) along the year (represented in months). All causes of fever had a seasonal distribution except for respiratory infections and bacterial AUFI. AUFI: acute undifferentiated febrile illness; SoI: source of infection; TD: travelers' diarrhea.

Main destinations of patients diagnosed with bacterial AUFI were Africa (27/82, 32.9%), SEA (26/82, 31.7%) and the Americas (19/82, 23.2%). Two-thirds (6/9) of AUFI coming from European countries were also diagnosed with bacterial AUFI. Among patients diagnosed with rickettsiosis, 20/46 (43.5%) came from Africa. Other relevant destinations were SEA (12/46, 26.1%) and the Americas (10/46, 21.7%). Patients diagnosed with leptospirosis mainly came from the Americas (9/21, 42.9%)

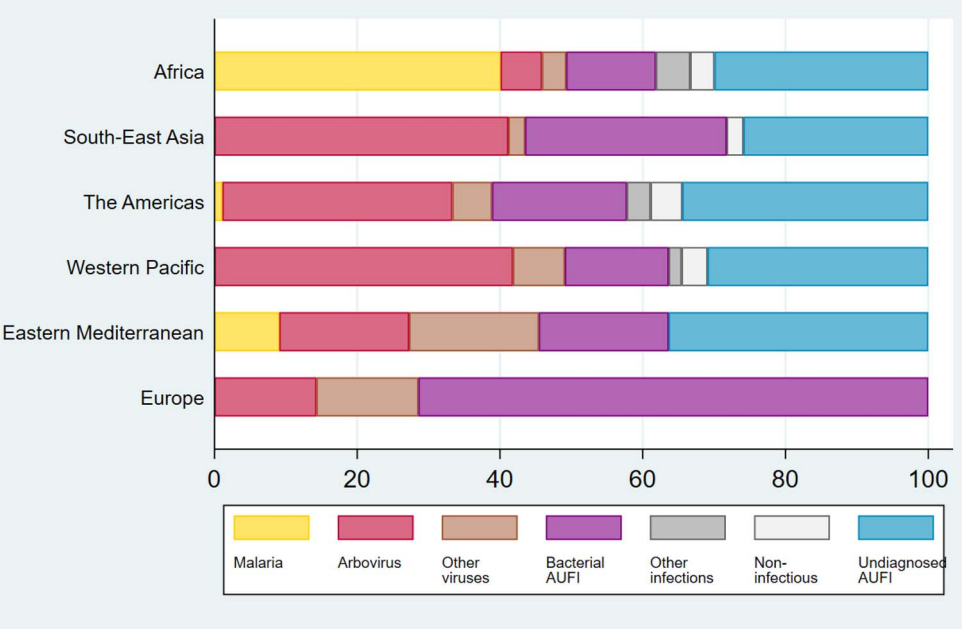

Figure 2. Distribution of the main acute undifferentiated febrile illness (AUFI) groups by WHO regions.

and SEA (7/21, 33.3%) and most of the enteric fever cases (5/6, 83.3%) came from SEA. Globally, bacterial AUFI did not show a clear seasonality (Figure 1).

Except for Europe (1/9, 6.7%), the proportion of undiagnosed AUFI was similar in all WHO regions, ranging from 25.0% to 34.7% ($P = 0.744$).

Predictive factors

Predictors of the leading causes of AUFI (malaria, arboviruses and bacterial AUFI) were estimated. LR+, LR− and aOR for variables associated with the aforementioned causes of AUFI are shown in Table 4.

Malaria predictive factors. Malaria cases ($n = 96$) were compared with patients with non-malarial fevers ($n = 669$). Highest LR+ for diagnosis of malaria were: hyperbilirubinemia (>1.2 mg/dL) (LR+ 9.1), thrombocytopenia ($<140\times10^9$/L) (LR+ 7.0) and splenomegaly (LR+ 7.0). Regarding LR−, returning from other places than Africa (LR− 0.05) and the absence of thrombocytopenia (LR− 0.20) strongly reduced the probability of malaria.

Using multivariate analysis, travelling to the WHO African region [aOR = 643.8, 95%CI: 46.7–8877.7, $p < 0.001$], VFRs (aOR = 48.3, 95%CI: 8.6–270.9, $p < 0.001$) and not taking antimalarial chemoprophylaxis (aOR = 8.1, 95%CI: 1.5–43.6, $p = 0.015$) were independently associated with malaria. Laboratory variables independently associated with malaria were thrombocytopenia (aOR = 65.1, 95%CI: 12.3–344.9, $p < 0.001$), hyperbilirubinemia (aOR = 24.3, 95%CI: 4.9–120.4, $p < 0.001$) and elevated CRP levels (>1 mg/dL) (aOR = 7.7, 95%CI: 1.5–39.6, $p = 0.014$).

Predictive factors of arboviruses. Patients diagnosed with arboviruses ($n = 108$) were compared with patients with the rest of the cohort ($n = 657$). The highest LR+ for arboviruses were: rash (LR+ 4.8), leucopenia ($<4.0\times10^9$/L) (LR+ 4.4) and neutropenia ($<2.4\times10^9$/L) (LR+ 3.6). After a multivariate analysis, skin rash (aOR = 9.0, 95%CI: 5.3–13.4, $p < 0.001$), retro-orbital pain (aOR = 2.1, 95%CI: 1.2–3.6, $p = 0.012$), neutropenia (aOR = 5.5, 95%CI: 3.2–9.4, $p < 0.001$) and lymphopenia ($<0.9\times10^9$/L) (aOR = 2.8, 95%CI: 1.6–4.7, $p < 0.001$) were independently associated with arboviral infections.

Bacterial AUFI predictive factors. Patients diagnosed with bacterial AUFI ($n = 82$) were compared with the remaining febrile patients ($n = 683$). Using multivariate analysis, predictors of bacterial AUFI were: (i) eschar (aOR = 189.9, 95%CI: 24.3–1486.1, $p < 0.001$), (ii) contact with fresh water (aOR = 2.2, 95%CI: 1.2–3.8, $p = 0.007$), (iii) trip to/within WHO European region (aOR = 4.8, 95%CI: 1.1–20.2, $p = 0.033$); (iv) non-VFRs (aOR = 6.1, 95%CI: 1.4–25.7, $p = 0{\cdot}014$) and (v) cytolysis (defined as AST or ALT > 40 IU/L) (aOR = 2.4, 95%CI: 1.4–4.2, $p = 0.021$).

Follow-up and outcomes

Overall, 63/765 (8.2%) patients were lost to follow-up, with no differences between patients presenting with focal symptoms and AUFI ($p = 0.458$). No patient died during the study period.

Median duration of fever differed between groups, being 5 days (IQR: 3–8) in patients with AUFI and 3 days (IQR: 2–7) in patients with SoI ($p < 0.001$). Consistently, the percentage of patients with fever at day 3 and 7 after the initial visit was 23.2% and 6.7% in the AUFI group and 12.5% and 3.5% in the SoI group ($p = 0.002$ and $p = 0.073$, respectively). After 28 days of follow-up, 8/723 (1.1%) patients still had fever, all of them belonging to the AUFI group: melioidosis ($n = 1$), histoplasmosis ($n = 1$), neuroendocrine tumor ($n = 1$), hemophagocytic syndrome ($n = 1$), measles ($n = 1$), undiagnosed AUFI ($n = 3$).

About 180/765 (23.8%) of patients were admitted to hospital: 28.9% in the AUFI group and 11.6% in the group of fevers

Table 4. Bivariate and multivariate analysis of risk factors associated with the main causes of acute undifferentiated febrile illness (AUFI)

		Bivariate analysis			Multivariate analysis		Likelihood ratios (LR)	
Malaria	Cases ($n = 96$)	Controls ($n = 669$)	OR (95%CI)	*p*-value	aOR (95%CI)	*p*-value	*LR*+	*LR*−
Male sex	71 (74.0)	335 (50.1)	2.83 (1.75–4.58)	<0.001	–	–	1.48	0.52
Age	40.5 (31–50.5)	36 (28–47)	1.02 (1.00–1.04)	0.006[a]	–	–	–	–
VFR	56 (58.3)	77 (11.5)	10.76 (6.73–17.22)	<0.001	48.31 (8.62–270.85)	<0.001	5.07	0.47
Africa	93 (96.9)	238 (35.6)	56.14 (17.59–179.17)	<0.001[b]	643.78 (46.69–8877.73)	<0.001	2.72	0.05
No antimalarial chemoprophylaxis	84 (87.5)	503 (78.0)	1.98 (1.05–3.72)	0.032	8.09 (1.50–43.55)	0.015	1.12	0.57
Headache	75 (78.1)	439 (65.2)	1.87 (1.12–3.11)	0.015	–	–	1.19	0.64
Vomiting	25 (26.0)	106 (15·8)	1.87 (1.13–3.09)	0.013	–	–	1.64	0.88
Hepatomegaly	10 (10.4)	18 (2.7)	4.21 (1.88–9.41)	<0.001	–	–	3.87	0.92
Splenomegaly	4 (4.2)	4 (0.6)	7.22 (1.78–29.40)	0.011[b]	–	–	6.97	0.96
Leucopenia ($<4 \times 10^9$/L)	26 (28.3)	115 (17.9)	1.81 (1.10–2.97)	0.018	–	–	1.58	0.87
Lymphopenia ($<0{\cdot}9 \times 10^9$/L)	52 (59.1)	197 (31.6)	3.12 (1.98–4.93)	<0.001	–	–	1.87	0.60
Thrombocytopenia ($<140 \times 10^9$/L)	62 (67.4)	61 (9.6)	19.45 (11.68–32.37)	<0.001	65.13 (12.30–344.87)	<0·001	7.02	0.36
Anemia (<12 mg/dL)	26 (27.7)	44 (6.9)	5.18 (3.00–8.94)	<0.001	–	–	4.02	0.78
Elevated CRP (>1 mg/dL)	80 (93.0)	391 (65.4)	7.06 (3.03–16.46)	<0.001	7.73 (1.51–39.57)	0.014	1.42	0.20
Elevated transaminases*	70 (74.5)	243 (40.0)	4.37 (2.67–7.14)	<0.001	–	–	1.86	0.43
LDH (>234 IU/L)	44 (74.6)	127 (31.0)	6.54 (3.51–12.18)	<0.001	–	–	2.41	0.37
Hyperbilirubinemia (>1.2 mg/dL)	52 (60.5)	36 (6.7)	21.45 (12.39–37.14)	<0.001	24.30 (4.91–120.38)	<0.001	9.09	0.42
Arbovirus	($n = 108$)	($n = 657$)						
South-East Asia	42 (38.9)	138 (21.0)	2.39 (1.56–3.68)	<0.001	–	–	1.85	0.77
Western Pacific	28 (25.9)	82 (12.5)	2.45 (1.51–4.00)	<0.001	–	–	2.08	0.85
Retro-orbital pain	49 (45.4)	107 (16.3)	4.27 (2.77–6.57)	<0.001	2.05 (1.17–3.59)	0.012	2.79	0.65
Myalgia	74 (68.5)	333 (50.7)	2.12 (1.37–3.27)	0.001	–	–	1.35	0.64
Arthralgia	47 (43.5)	204 (31.1)	1.71 (1.13–2.59)	0.011	–	–	1.40	0.82
Rash	73 (67.6)	93 (14.2)	12.65 (7.99–20.01)	<0.001	8.98 (5.25–13.36)	<0.001	4.78	0.38
Leucopenia ($<4 \times 10^9$/L)	60 (56.1)	81 (12.9)	8.62 (5.51–13.49)	<0.001	–	–	4.35	0.50
Neutropenia ($<2{\cdot}5 \times 10^9$/L)	67 (63.2)	107 (17.7)	8.00 (5.12–12.50)	<0.001	5.50 (3.23–9.38)	<0.001	3.57	0.45
Lymphopenia ($<0{\cdot}9 \times 10^9$/L)	70 (66.0)	179 (29.6)	4.63 (2.99–7.17)	<0.001	2.75 (1.61–4.68)	<0.001	2.23	0.48
Thrombocytopenia ($<140 \times 10^9$/L)	38 (35.5)	85 (13.7)	3.47 (2.19–5.48)	<0.001	–	–	2.59	0.75
Cytolysis (AST or ALT > 40 IU/L)	52 (49.1)	196 (32.9)	1.96 (1.29–2.98)	0·001	–	–	1.49	0.76
Bacteria	($n = 82$)	($n = 683$)						
Male sex	54 (65.85)	352 (51.54)	1.81 (1.12–2.93)	0.014	–	–	1.28	0.70
Non-VFR	79 (96.34)	553 (80.97)	6.19 (1.92–19.92)	<0.001[b]	6.08 (1.44–25.66)	0.014	1.19	0.19
Europe	6 (7.32)	9 (1.32)	5.91 (2.05–17.06)	<0.001	4.79 (1.14–20.20)	0.033	5.55	0.94
Rural area	76 (92.68)	558 (81.70)	2.84 (1321–6.66)	0.013	–	–	1.13	0.40
Contact with animals	37 (46.25)	199 (30.02)	2.61 (1.25–3.21)	0.003	–	–	1.54	0.77
Fresh water exposure	45 (46.25)	233 (34.72)	2.29 (1.44–3.63)	<0.001	2.17 (1.24–3.80)	0.007	1.58	0.69
Tick bite	12 (15.38)	24 (3.65)	4.80 (2.30–10.05)	<0.001	–	–	4.22	0.88
Eschar	20 (24.39)	1 (0.15)	220.00 (29.04–1666.94)	<0.001[b]	189.86 (24.25–1486.13)	<0.001	166.58	0.76
Myalgia	53 (64.63)	354 (51.83)	1.70 (1.05–2.74)	0.028	–	–	1.25	0.73
Cytolysis (AST or ALT > 40 IU/L)	38 (46.91)	210 (33.87)	1.73 (1.08–2.75)	0.021	2.38 (1.36–4.16)	0.002	1.39	0.80

[a]Wilcoxon rank sum test. [b] Fisher's exact test.
*Elevated transaminases defined as an elevation of AST (> 40 IU/L), ALT (> 40 IU/L), GGT (> 40 IU/L) or alkaline phosphatase (>116 IU/L).

with SoI ($p < 0.001$); these differences between groups were consistent even after excluding malaria cases (19.8% vs. 11.7%, $p = 0.009$). Admission to ICU was also more common in patients with AUFI than in patients with SoI (4.9% vs. 0.4%, $p < 0.001$). Among admitted patients, 144/180 (80.0%) presented at least one criteria of complicated imported fever. Patients with AUFI had a higher proportion of complicated disease than those with SoI (55.0% vs. 39.4%, $p < 0.001$). These differences were similarly observed after excluding malaria cases (49.0% vs. 39.4%, $p = 0.012$).

Discussion

In our cohort, over 40% of travelers with AUFI were diagnosed with malaria or dengue, infections that can be easily diagnosed by RDT. Arboviruses were more common than malaria and almost 75% of them were diagnosed during *Aedes* spp. highest activity months. This is particularly relevant in areas at risk of introduction of these pathogens. Moreover, one-third of patients remained undiagnosed with standard diagnostic methods.

Among returning travelers with fever, patients with AUFI presented with more severe disease than those with a clear SoI, with longer duration of fever and higher hospital and ICU admission rates, even after excluding malaria cases. Moreover, AUFI are more difficult to diagnose at initial visit and prompt an increased number of diagnostic tests. Therefore, efforts towards achieving a prompt diagnosis and an adequate treatment for AUFI have to be a priority in the management of fever in returning travelers.

Febrile travelers with SoI were mainly diagnosed with TD or respiratory infections. Bacterial enteritis resulted in the main cause of TD, accounting for >50% of cases in all WHO regions. This calls for the use of empirical antibiotic treatment in patients with febrile TD. In our cohort, respiratory viruses PCRs on nasopharyngeal swabs showed to be relevant diagnostic tools in travelers with fever, achieving a microbiological confirmation in three-quarters of cases in which they were performed. These data reinforce the importance of performing nasopharyngeal swabs in patients with imported fever to avoid further investigations and unnecessary antibiotic treatments.

In our cohort, arboviruses were the main cause of AUFI, accounting for almost one-quarter of cases and being more common in travelers returning from SEA, Western Pacific and the Americas. Arboviral diseases were the main cause of AUFI in all WHO regions except for malaria in Africa and bacterial infections in Europe. Particularly, dengue caused 20% of AUFI cases and 12% of all febrile travelers. These results contrast with most of the previous studies that consistently described malaria as the main tropical infection in returning travelers with fever and stated seroconversion rates of dengue in 1.0–6.8%.[2–5,13–17] Moreover, a recent systematic review found dengue as the causative agent of only 5.2% of patients with imported fever.[2] Most studies of imported fever reporting a dengue incidence >10% evaluated travelers mainly returning from Asia and SEA[15,18] or did not include undiagnosed cases.[5] Some factors that could explain our findings are the systematic search of arboviral infections in the study participants, the use of different diagnostic tests for arboviruses (RDT, serology and PCR) and the increasing incidence of arboviral infections in some endemic areas due to climate change and deforestation, population movements and introduction of vectors into new areas, amongst other.[6,19] However, the recent breakdown in control strategies for malaria due to COVID-19 is likely to modify the incidence of the leading causes of imported fever in the following years.[20]

In our study, over 40% of returning travelers with AUFI were diagnosed with malaria or dengue, diseases that can be diagnosed with RDTs very easily and quickly, with little resources. These tests should be standard in emergency wards of primary care facilities that deal with returning travelers.[21] Alternatively, factors associated with the main causes of AUFI (such as traveling to Africa, VFR, non-antimalarial chemoprophylaxis, thrombocytopenia, hyperbilirubinemia, elevated CRP and splenomegaly for malaria; and rash, retro-orbital pain, leucopenia, neutropenia and lymphopenia for arboviral infections) may rise the clinical suspicion of these entities by healthcare professionals with no direct access to those specific diagnostic tests.[2–4,8,16,17,22–24] In these sense, the creation of networks including specialized centers where patients with imported fever could be referred to would be highly recommended.

Implementation of RDTs is also crucial from a public health perspective.[2] Due to the presence of different species of *Aedes* spp., some European regions are at high risk of introduction of some arboviruses, especially given that almost 75% of imported arboviral infections were diagnosed during the months of mosquito's highest activity.[9–11] Indeed, in the last years, several outbreaks of non-imported cases of Dengue, Chikungunya and Zika viruses have been reported in France, Spain, Italy, Portugal and Croatia.[11] Current control strategies for the introduction of arboviruses are based on the notification of all suspected cases that are (in the absence of RDT) almost all travelers presenting with fever or rash.[10,24] Clinical and laboratory notification of these cases to the public health agencies prompts the mosquito services response, triggering mosquito density control strategies around risk areas. Furthermore, risk of reintroduction of malaria is not negligible in some Mediterranean countries like Greece.[19,25,26] New multiplex RDTs including malaria, dengue and other arboviral infections would allow directing efforts to confirmed arboviral and malarial cases, allowing better targeted vector control interventions.[27]

We also need better diagnostic tools to improve the management of AUFI as up to one-third of patients with AUFI remained undiagnosed and almost half of bacterial AUFI could not be microbiologically confirmed (thus being considered probable cases). Undiagnosed AUFI had a laboratory presentation similar to bacterial infections. Therefore, it seems likely that undiagnosed AUFI are caused by a diverse range of bacterial infections that, due to the lack of available sensitive and specific standard diagnostic methods, cannot be properly identified. Interestingly, the main bacterial infections identified among patients with AUFI were rickettsioses, leptospirosis and enteric fever.[2,3,5,28] Risk factors for bacterial AUFI included travelers not visiting friends and relatives, contact with fresh water, presenting with an eschar or cytolysis.[2,3,28] Some of these risk factors are strongly associated with specific bacterial infections, most of them susceptible to azithromycin or doxycycline.[29] From our results, empirical antibiotic treatment should be considered in all patients with AUFI after ruling out malaria and arboviral infections, especially when presenting the aforementioned risk factors. Interestingly, coming from European countries was a risk factor independently

associated with bacterial AUFI. This fact reinforces the idea of emergence and reemergence of these infections in regions like Europe and questions the division in tropical and non-tropical causes of imported fever.[30,31]

This study has some limitations. First, it is uncertain how the COVID-19 pandemic can affect these figures, not only because it could be established as a cause of imported fever, but also because of its influence on control strategies of some of other causes of fever in endemic areas. Current algorithms should include diagnostic tests for SARS-CoV-2 in the initial management of patients with imported fever. Second, study participants were recruited at three European referral centers. Consequently, travelers from other regions and patients with less severe diseases or self-limited presentations attending less specialized healthcare facilities might not be fully represented, as will not those pathogens not included in the diagnostic work-up. Pathogens with long incubation periods and infections in which fever is not part of the common clinical presentation might also be underrepresented. Moreover, given the incubation period of some pathogens, we cannot rule out that some infections could be acquired before or after the travel. Finally, predictors of arboviral infections mainly showed characteristics associated with dengue fever. Thus, prediction of non-dengue arboviruses based on these factors could be inaccurate due to the low number of cases.

Based on our results, malaria and dengue RDTs should be promoted for the diagnosis of travelers with AUFI since their use can provide a rapid and reliable diagnosis in almost half of cases. This is particularly relevant in areas at risk of introduction of vector borne diseases in which control strategies should be improved. Empirical antibiotic regimens including drugs active against intracellular bacteria such as azithromycin or doxycycline should be considered in patients with AUFI, after ruling out malaria and arboviruses. Implementation of new diagnostic tools such new genome sequencing is crucial to improve the diagnosis of AUFI since one-third of cases remain undiagnosed using routine diagnostic methods.

Supplementary Data

Supplementary Data are available at *JTMEDI* Online.

Authors Contributions

D.C.F., B.G., E.B., V.d.A., J.L.G., C.R., J.M. designed the study. D.C.F., L.C., S.V.D.B., B.G., E.B., N.R.V., A.A.R., L.B.S., I.V., N.F. recruited the study participants and collected the data. C.S., M.F.P. did the data entry. M.J.M., J.N.C., D.C., M.V.E. did the laboratory work. D.C.F. performed the statistical analysis. D.C.F., L.C., S.V.D.B., B.G., E.B., J.M. discussed the results. D.C.F. wrote the manuscript, did the figures and tables. All the authors critically reviewed the manuscript.

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Conflict of Interest

None declared.

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