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REVIEW

Rickettsioses and Q fever in travelers (2004–2013)

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Summary Rickettsioses (also called typhus) are associated with arthropods, including ticks, mites, fleas, and lice, although Q fever is more frequently acquired through the inhalation of contaminated aerosols or the consumption of milk. These zoonoses first emerged in the field of travel medicine 20 years ago. Here, we review rickettsioses and Q fever in travelers, highlighting cases reported in the past decade. African tick bite fever and Mediterranean spotted fever are the two most frequent spotted fevers. While the presentation of these fevers is typically benign, cardiac and neurological complications due to African tick bite fever have been reported, and Mediterranean spotted fever has been complicated by multi-organ failure and death in a few cases. Murine typhus and Q fever remain difficult to recognize and diagnose because these illnesses often present with only fever. New molecular tools, particularly when deployed with samples obtained from eschar swabs, might be easily implemented in laboratories with PCR facilities. Doxycycline must be introduced upon clinical suspicion of rickettsioses or Q fever and should be considered in cases of fever of unknown origin in travelers who are returning from at-risk geographic areas.

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1. Introduction

Rickettsioses (also called typhus) are infectious diseases caused by obligate intracellular bacteria of the order Rickettsiales. These organisms have long been described as short, Gram-negative rods that retain basic fuchsin when stained using the Gimenez method. In recent years, the taxonomy of rickettsiae has been reorganized and continues to be modified as new data become available [1,2]. Four groups of diseases, however, are still commonly called rickettsioses. These diseases are attributable to bacteria of the genus *Rickettsia*, including the spotted fever group, the typhus group, the *Rickettsia bellii* group, and the *Rickettsia canadensis* group of the family Rickettsiaceae; scrub typhus resulting from *Orientia tsutsugamushi* (formerly named *Rickettsia tsutsugamushi*); human ehrlichioses and anaplasmosis attributable to bacteria from the family Anaplasmataceae; and the ubiquitous Q fever resulting from *Coxiella burnetii*, which has recently been removed from the order Rickettsiales [1,2].

Agents of rickettsioses are associated with arthropods, including ticks, mites, fleas, and lice, which act as vectors, reservoirs, and/or amplifiers of the bacteria. Thus, exposure to these diseases has been closely associated with exposure to the associated arthropod vectors. Notably, most of these vectors favor specific optimal environmental conditions, biotopes, and hosts. These factors determine the geographical distribution of the vectors and consequently the risk areas for the diseases [1,2] (Fig. 1).

International travel has increased 50% over the past decade, with 983 million tourist arrivals in 2011 [3]. This increase continued in 2012, with more than 1.035 billion tourist arrivals and 298 million international tourists globally between January and April 2013; this number was 12 million more than that for the same period in 2012, according to United Nations World Tourism Organization [4]. Primary reasons for travel are tourism, business, visiting friends and relatives, and other reasons that include studies or military, missionary, or foreign aid deployment. These travelers might be exposed to vector bites and thus rickettsioses.

In recent years, the importance of rickettsioses have become apparent in the field of travel medicine, as increasing numbers of individuals are being exposed (e.g., African tick bite fever in travelers returned from sub-Saharan Africa) [1]. In 2004, Jensenius et al. [5] reported more than 450 rickettsioses cases among travelers. In 2006, Bottieau et al. [6] reported that among 1842 ill and febrile returned travelers (2000—2005), 53 individuals had a spotted fever group (SFG) rickettsiosis, four individuals had murine typhus, three individuals had scrub typhus and 13 individuals had Q fever. More recently, rickettsial diseases have been reported in 280 returned international travelers, according to the GeoSentinel surveillance network from 1996 to 2008. Among these 280 travelers, 231 individuals had spotted fever rickettsioses (197 SFG rickettsiosis cases were acquired in sub-Saharan Africa), 10 individuals had typhus group rickettsioses, and 16 individuals had scrub typhus, including one fatal case of scrub typhus encephalitis acquired in Thailand [7]. Additionally, based on GeoSentinel, approximately 300 cases of travel-associated rickettsioses were reported in 2013 for the 2007—2011 period (267 cases of tick-borne spotted fever rickettsioses, 17 cases of murine typhus and 14 cases of scrub typhus) among more than 47,000 returned ill travelers [3].

In the past decade, knowledge in the field of rickettsioses has evolved (Table 1). New diagnostic methods have been developed for describing emerging rickettsioses. The role of rickettsioses in the so-called "fever of unknown origin" throughout the world and in ill returned travelers has also been recently highlighted [1].

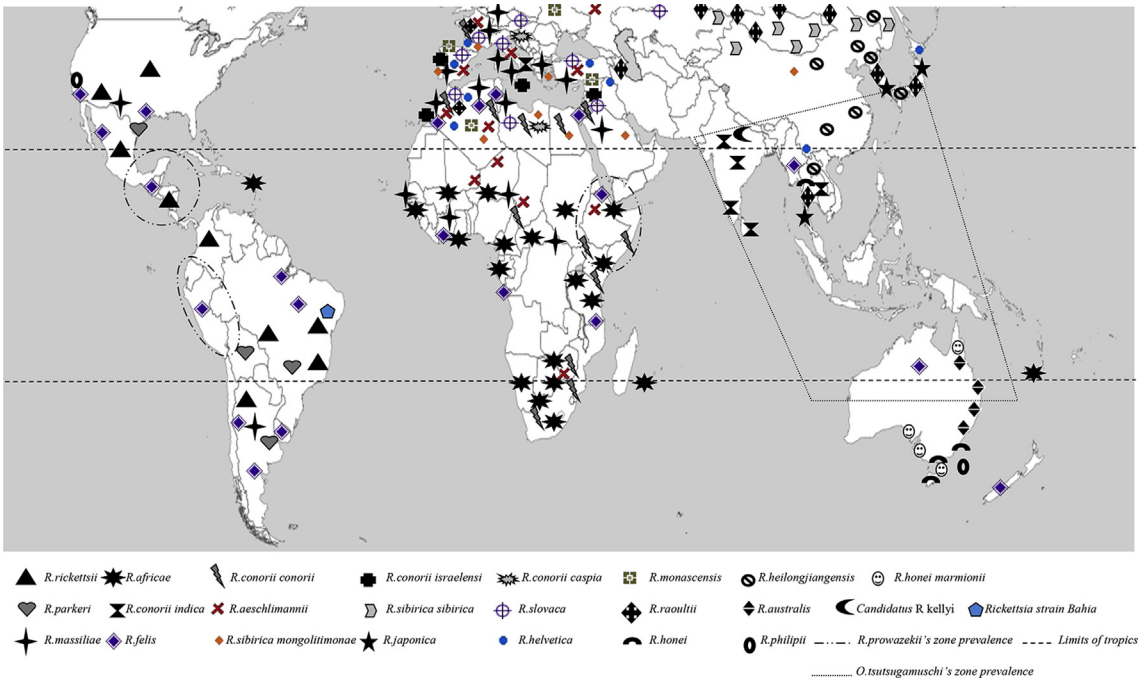

Figure 1 Geographic distribution of rickettsial diseases agents. Note that murine typhus from *R. typhi* is ubiquitous.

Table 1 Rickettsioses in travelers since 2004 [1].

Diseases	Agents	Geographic areas	Symptoms
African tick bite fever	*Rickettsia africae*	Sub-Saharan Africa West Indies	Incubation period: 5—10 days. Fever and flu-like symptoms. One or multiple eschars Lymphadenitis. Rash
Mediterranean spotted fever	*Rickettsia conorii conorii*	Mediterranean areas Sub-Saharan Africa, northern and central Europe	Incubation period: 6—10 days. Abrupt fever, an eschar. Maculopapular rash involving the palms and soles. Unilateral or bilateral conjunctivitis. potential severe
Rocky mountain spotted fever	*Rickettsia rickettsii*	North, central and south America	Incubation 5—10 days. High fever. Severe frontal headache, chills and myalgia. Anorexia, nausea, vomiting, abdominal pain, diarrhea, photophobia and cough. Rash appears as small, pink, blanching macules that evolve maculopapules. No eschar. potentially severe
Tick borne spotted fever	*Rickettsia massiliae*	Europe, South America, Asia and sub-Saharan Africa	Fever, chills, malaise, rash.
Israeli spotted fever	*Rickettsia conorii Israelensis*	Israel, Sicilia, Portugal	Fever, rash, asthenia.
SENLAT (scalp eschars and neck lymphadenopathy after tick bites)	*Rickettsia slovaca* *Rickettsia raoultii*	Europe	Asthenia, headache, painful adenopathies, a painful scalp eschar surrounded by a perilesional erythematous halo. Alopecia around the eschar that lasts for several months. Chronic asthenia.
lymphangitis-associated rickettsiosis (LAR)	*Rickettsia sibirica mongolitimonae*	Europe, sub-Saharan Africa and North Africa	Fever, headache, myalgia, cutaneous rash, enlarged lymph nodes and/or lymphangitis, and single or multiple inoculation eschars.
Tick borne spotted fever	*R. parkeri*	North, central and south America	Necrotic inoculation eschar. Low to moderate fever
Indian tick typhus	*R. conorii indica*	India, Thailand, Laos	Rash, purpura. Fever.
Murine typhus	*Rickettsia typhi*	Worldwide distribution, coastal tropical and subtropical regions	Fever, headache, chills, cough, myalgia, nausea, abdominal pain and rash hepatomegaly.
Epidemic typhus Brill-Zinsser disease	*Rickettsia prowazekii*	Body louse-infested environments	Fever, headache, and myalgia. Nausea vomiting, cough, and abnormalities of the central nervous system function: stupor to coma. Diarrhea, pulmonary involvement, myocarditis, splenomegaly, and conjunctivitis. Rush.
Scrub typhus	*Orientia tsutsugamushi*	South and southeastern Asia Pacific	Fever, lymphadenitis, a macular rash and an eschar. Pneumonitis, meningo-encephalitis. Fatality rate 10% unless treated appropriately.
Acute Q Fever	*Coxiella burnetii*	Worldwide distribution	Fever of unknown origin hepatitis. Pneumonitis.

The objective of this article is to systematically review cases of travel-related rickettsioses reported in the past 10 years to inform clinicians of the methods used to recognize, diagnose and treat rickettsioses in returning travelers. We performed a literature search in the PUBMED database by cross-referencing the followings terms: "rickettsia", "typhus", "murine typhus", "epidemic typhus", "scrub typhus", "acute Q fever", and "ehrlichioses", and the causative agents of these rickettsioses, and "travel", "travelers", and "imported diseases". This literature search was restricted to reports from 2004 to 2013, as the last major review on this topic was published in 2004.

2. Tick-borne spotted fever group rickettsioses

Tick-borne rickettsioses result from obligate intracellular bacteria belonging to the SFG of the genus *Rickettsia*. These zoonoses are among the oldest-known vector-borne diseases. However, the scope and importance of recognized tick-associated rickettsial pathogens have increased dramatically in the past 25 years, making this complex of diseases an ideal paradigm to understand emerging and reemerging infections. Several species of tick-borne rickettsiae considered nonpathogenic for decades have now been associated with human infection [1]. Tick-borne spotted fever group rickettsioses share common clinical signs. After an incubation period of 6—10 days, the clinical course might include abrupt fever, one or several eschars at the tick-bite site, a maculopapular or vesicular rash involving the palms and soles and a flu-like syndrome. Eschars and rash are the hallmarks of tick-borne rickettsioses and key clinical indicators for diagnosis, but these symptoms might be absent.

2.1. African tick bite fever

African tick bite fever (ATBF) is caused by *Rickettsia africae*. This disease and its agent are endemic in sub-Saharan Africa and in the West Indies, including many Caribbean islands. ATBF is transmitted through *Amblyomma* ticks, primarily *Amblyomma hebraeum* and *Amblyomma variegatum* (Fig. 2). The rate of ticks that harbor *R. africae* in nature is high, up to 100%. Furthermore, these ticks are aggressive, and numerous ticks can simultaneously attack a potential host, including humans. Thus, cases of African tick-bite fever often occur in clusters among subjects entering the bush during a safari [1,2]. Game hunting, travel to southern Africa, and travel during November through April have been shown as independent risk factors for ATBF.

Figure 2 Two female tick vectors of spotted fever group rickettsioses in travelers. left: *Amblyomma variegatum*, vector of *R. africae*, the agent of ATBF. right: *Rhipicephalus sanguineus*, the primary vector of *R. conorii conorii*, the agent of Mediterranean spotted fever.

ATBF has been reported as the second most common documented etiology of fever documented in ill travelers returning from sub-Saharan Africa, after malaria [3]. By 2004, more than 350 travel-associated cases of African tick bite fever have been reported in travelers originating from Europe, North America, Australia, Argentina and Japan [5,8]. Most patients were infected in South Africa, where many popular wildlife attractions are highly endemic for *R. africae* infection. African tick bite fever has been reported in a wide spectrum of travelers, particularly tourists, game hunters, and deployed soldiers [8].

In the past 10 years, more than 100 cases of ATBF have been reported in the literature. All individuals had traveled to sub-Saharan Africa, and 81% (86/106) of these travelers stayed in South Africa. Other visited countries included Swaziland (14%, 15/106), Zimbabwe (2.8%, 3/106), Botswana and Malawi (1.8%, 2/106), and Namibia, Zambia, Ethiopia and Gambia (0.9%, 1/106). Eighty-seven percent of travelers were from Europe (France, The Netherlands, Switzerland, Spain, United Kingdom and Sweden). Other travelers were from the USA, Australia, Israel and Taiwan [9—15]. Clusters of cases were frequent, with 6 groups of tourists attacked by ticks during safaris [14,16—20].

Typical clinical presentations with multiple eschars and vesicular or maculopapular rashes (76.5%), were most frequent [11,13,14,18,21—27]. Infections with only one eschar (18%) have also been reported [12,19,28—30]. In two cases, the eschar was unusually located on the genitals. In one case, the eschar was not observed during the initial examination [31], and in another case the presence of an eschar led to misdiagnosis (due to the presence of genital ulceration and febrile rash) [32]. Eschars were not reported in 10% of cases [17,18,33,34]. Interestingly, new clinical findings have been reported. Neurological complications have been reported in 6.6% of cases, involving irritability and depressed mood [17]; six other cases involved paresthesia and motor weakness, hemifacial pain and paresthesia and unilateral sensorineural hearing loss [35], and internuclear ophthalmoplegia was reported in one case [33]. Cardiac complications were also reported with the description of the first case of myocarditis associated with ATBF in a German traveler to Swaziland [36]. Coinfection with other travel-associated infections has also been reported. Coinfection with *C. burnetii*, the agent of Q fever, was reported in a 56-year-old Swedish man returning from Gambia, who exhibited fever, headache and myalgia without skin lesions or eschars [34]. Another case of coinfection with leishmaniasis and ATBF was reported in a 52-year-old American nurse evaluated for a well-demarcated, tender, shallow ulcer on her wrist after travel to Botswana. This individual reported being scratched on the ankle by a gnat. Cutaneous biopsy showed leishmania promastigotes of *Leishmania tropica*, and the diagnosis of ATBF was based on serology [15]. Most of these

Figure 3 Typical case of African tick bite fever from *R. africae* involving a woman showing 2 typical eschars.

cases were diagnosed through serology or the PCR analysis of skin biopsies [9,12,28,37]. Several recent reports of ATBF cases have provided opportunities to highlight the use of PCR after eschar swabbing [13,38] (see below). Fig. 3 shows eschars on the left leg of a woman who presented fever and headache after a safari in Kruger National Park in South Africa; ATBF was first diagnosed after positive PCR using a sample from an eschar swab, and further confirmed through serology.

2.2. Mediterranean spotted fever

Mediterranean Spotted Fever (MSF) is caused by *Rickettsia conorii conorii* and transmitted through the brown dog tick *Rhipicephalus sanguineus*. MSF is endemic in all Mediterranean areas, and sporadic cases have been reported in sub-Saharan Africa, northern and central Europe, and Asia [1]. In Europe, most MSF cases occur in the summer. In particular, this higher incidence during warmer months might reflect a warming-mediated increase in the aggressiveness of *R. sanguineus* ticks, causing these parasites to bite humans [39]. Locals and travelers in the Mediterranean area are particularly targeted during July and August.

Unilateral or bilateral conjunctivitis might represent the eye-inoculation site of the rickettsia (instead of an eschar), occurring after the manipulation of crushed infected ticks. Gastrointestinal symptoms might be present in approximately 30% of patients, however these symptoms are more likely observed in children. Multiple eschars and clusters of MSF cases have been reported, representing novel findings for MSF because the probability of being bitten simultaneously through several infected *R. sanguineus* ticks is low [1,2]. Complications are not uncommon and include neurological involvement, peripheral gangrene, and respiratory distress syndrome. Thus, MSF could be fatal. The mortality rate with treatment is estimated between 2% and 5% [1], although in Portugal, mortality has recently affected 13% of MSF patients [1].

In 2004, Jensenius et al. [5] reported 35 cases of MSF in travelers from northern Europe and North America. The majority of individuals were infected in the Mediterranean area. Few cases were acquired in sub-Saharan Africa. Most travel-associated cases were mild and uncomplicated, but visual loss was reported in a British traveler returning from Africa, and a 39-year-old U.S. missionary deployed to Kenya died of multi-organ failure despite prompt medical attention at a local hospital [5].

Since 2004, more cases have been reported. Countries of exposure have included Morocco, Algeria, South Africa, Portugal, Spain, Kenya and Turkey [40—44], with travelers originating from Europe (Belgium, France, United Kingdom, Czech Republic, and Portugal), South Africa and Japan. Eschars have not been described for seven of the nine travelers reported [40,41,43,45]. The characteristics and symptoms of the patients are listed in Table 2.

We recently diagnosed two additional MSF cases. The first case involved a 72-year-old woman who presented a with high fever, a maculopapular rash involving the trunk, an eschar on the abdomen, clear purpura on the lower limbs, arthralgia, myalgia and severe abdominal pain one week after returning from a 2-week visit to Algeria. Evolution was favorable after doxycycline treatment. The disease was diagnosed through immunofluorescence assay. The second case involved a 53-year-old woman who presented with a high fever, a generalized maculopapular rash involving the entire body, palms, soles and face and purpura on the lower limbs after returning from a week-long holiday in Algeria. No eschar was observed (see Fig. 4). The

Table 2 Mediterranean spotted fever: characteristics and symptoms of ill returned travelers reported since 2004.

Authors	Patients, age	Visited countries	Eschar	Rash	Complications	Death
Freibergerova et al. [42]	Czech woman, 25	Spain	Yes	Yes	No	No
Yoshikawa et al. [43]	Japonese man, 52	Kenya	No	Yes	No	No
Chipp et al. [44]	English woman, 56	Marocco	Yes	Yes	No	No
Laurent et al. [40]	Belgian man, 20	Marocco	No	Yes	No	No
Demeester et al. [41]	Belgian man, 49	Marocco	No	Yes	Encephalitis	No
	Belgian woman, 62	Marocco	No	Yes	Pulmonary embolism	No
	Belgian man, 61	Marocco	No	Yes	Multiorgan failure	No
De Almeida et al. [45]	South African man, 53	South Africa, but diagnostic in Brazil	No	Yes	Multiorgan failure	Yes
Two cases in our unit	French woman, 72	Algeria	Yes	Yes	No	No
	French woman, 53	Algeria	No	Yes	No	No
Total	Sex ratio 1,2	81% in Mediterranean area	30%	100%	40%	10%

Figure 4 Generalized maculopapular rash, including the face, palms, and soles, on a patient with Mediterranean spotted fever returned from Algeria.

diagnosis was confirmed through a positive *R. conorii conorii*-specific quantitative PCR assay of a skin biopsy sample. Evolution was favorable with doxycycline treatment.

2.3. Rocky mountain spotted fever

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii*. Rocky Mountain spotted fever is endemic to regions of North, Central and South America, in both rural and urban zones. The vectors of this bacteria include the Rocky Mountain wood tick (*Dermacentor andersoni*), the American dog tick (*Dermacentor variabilis*), the Cayenne tick (*Amblyomma cajennense*), and the brown dog tick (*R. sanguineus*) [1].

The incubation for RMSF is approximately 5—10 days, followed by the presentation of a high fever (39—41 °C), a severe frontal headache, chills and myalgia. Over the next few days, these symptoms continue and might be accompanied by anorexia, nausea, vomiting, abdominal pain, diarrhea, photophobia and cough. Rash, considered a hallmark of Rocky Mountain spotted fever, appears as small, pink, blanching macules that evolve maculopapules. Interestingly, no eschar is present. The entire body might be involved, including the mucous membranes of the palate and pharynx. The rash might include petechial lesions. In early studies, the mortality rate before the introduction of effective therapies was approximately 10% for children and 20% for adults. In recent studies, despite the availability of an effective treatment, an estimated 5—10% of US patients die from *R. rickettsii* infections. For unknown reasons, case-fatality rates in Central America are considerably higher, with estimates from recent outbreaks as high as 38% in Mexico and 100% in Panama [1].

Cases of RMSF are rarely reported in returned travelers. In 2004, Jensenius et al. [8] reported three probable cases occurring between 1988 and 2004. A German 24-year-old male fell ill 12 days after being bitten by a tick during a camping holiday in North Carolina. An American patient contracted RMSF in the USA but developed symptoms and was diagnosed while traveling in France; this patient had an inoculation eschar on the leg (making the diagnosis of RMSF less probable than another emerging rickettsiosis, such as *Rickettsia parkeri*). In 1992, a Finnish 48-year-old female fell ill with probable RMSF shortly after returning from a camping trip in the mid-western U.S [8].

In 2005, De Pender et al. [46] reported a case of an American traveler presenting fever, headache, purpuric rash and no eschar during a stay in the Netherlands. Rocky Mountain spotted fever was suspected partly because the traveler came from an endemic region (Georgia, USA), and evolution with doxycycline was favorable. Serology was positive. The potential seriousness of this rickettsiosis makes it important to understand this disease, despite its apparent rarity among travelers.

2.4. Other tick-borne rickettsioses

Many other tick-borne spotted fever group rickettsioses have been reported worldwide [1] (Fig. 1), and some diseases have been sporadically reported among international travelers. The median incubation period for all rickettsioses is approximately a week. Interestingly, case reports for travelers have provided opportunities to obtain better descriptions of some of these emerging diseases.

In 2004, Jensenius [8] reported a case of Indian Tick Typhus (*Rickettsia conorii indica*) in a 25-year-old French woman after an one-month stay in India, and a case of Astrakhan fever (*Rickettsia conorii caspia*) was reported for a 36-year-old French male who fell ill a few days after a bush walk in Chad in October 2000 [8], representing the first case reported outside Europe. Five cases of Siberian tick typhus, due to *Rickettsia sibirica sibirica*, have also been reported from Mongolia [8]. Additionally, an uncomplicated case of *Rickettsia aeschlimannii* infection from Morocco has also been reported [8].

Since 2004, one case of *Rickettsia massiliae* infection, three fatal cases of Israeli spotted fever, two cases of scalp eschars and neck lymphadenopathy after tick bites (SENLAT syndrome), one case of lymphangitis-associated rickettsiosis (LAR), two cases of *R. parkeri*, and one case of Indian tick typhus have been reported (Table 3).

R. massiliae is associated with *Rhipicephalus* ticks. This rickettsia is present in Europe, South America, Asia and sub-Saharan Africa. However, only one case has been reported in an Argentine tourist who was arrived in Spain with chills, malaise, fever and rash [47].

Table 3 Other tick borne rickettsioses: countries of exposure and complications by species.

Species	Origin of the patient, age	Visited countries	Complications
R. conorii israelensis	English woman, 63	Portugal	Septic shock-death
R. conorii israelensis	Swiss man, 63	Crete, Lybia, Malta	Death
R. conorii israelensis	Israeli man, 51	India	Death
R. slovaca	French woman, 58	Italia	No
R. slovaca	French woman, 23	Mongolia	No
R. slovaca	Swiss woman, 27	Corsica	No
R. sibirica mongolitimonae	French man, 52	Egypt	No
R. parkeri	American man, 51	Honduras	No
R. parkeri	Spanish man, 59	Uruguay	No
R. conorii subsp. *indica*	Australian man, 62	India	No
R. massiliae	Argentine woman, 56	In Spain	No

Israeli spotted fever is a Mediterranean-like spotted fever attributed to *Rickettsia conorii* subsp. *israelensis*, and this disease transmitted by *R. sanguineus*. Israeli spotted fever is present in Europe, Asia and North Africa [1]. Three fatal cases of Israeli spotted fever were reported in 2008 [48—50]. One case involve a Switzerland patient who acquired the infection after a Mediterranean cruise [49], while the second case involved a UK traveler returning from South Portugal [48], and the third case involved a traveler returning to Israel from India [50].

In January 2009, a 58-year-old woman presented in Marseille France, a few weeks after the start of a 2-month stay in the area of San Remo, Italy. The woman recalled a tick bite on the scalp and presented with an eschar on the site of the bite and cervical adenopathies. This syndrome has been known for a couple of years as TIBOLA (for tick-borne lymphadenopathy) or DEBONEL (for *Dermacentor*-borne necrotic erythema and lymphadenopathy) [1], and more recently SENLAT for Scalp Eschar and Neck Lymphadenopathy After Tick Bite has been described. Several SFG rickettsia, including *Rickettsia slovaca*, *Rickettsia raoultii* Candidatus *Rickettsia rioja*, and *Rickettsia sibirica mongolitimonae*, have been associated with this syndrome [1,51]. Interestingly, alopecia around the eschar that lasts for several months and prolonged or chronic asthenia often occur. In 2009, Jensenius et al. [7] reported two cases involving a French patient returning from Mongolia and a Swiss tourist returning from Corsica.

Lymphangitis-associated rickettsiosis (LAR) is attributable to *R. sibirica mongolitimonae*, and this disease is transmitted through *Hyalomma* spp. and *Rhipicephalus pusillus* ticks in Europe, sub-Saharan Africa and North Africa. Typical clinical signs include fever, headache, myalgia, cutaneous rash, enlarged lymph nodes and/or lymphangitis, and single or multiple inoculation eschars in the spring months in Mediterranean areas. No fatal cases have been observed, but complications, such as acute renal failure, retinal vasculitis, and lethargy with hyponatremia, have been noted [1]. In 2010, Socolovschi et al. [52] reported a case in an individual returning from a 2-week trip to Egypt, representing the first published case of a traveler with LAR.

R. parkeri infection is an emerging infection endemic in the United States and Central and South America. This infection is milder than RMSF, and no severe systemic manifestations or deaths have been described [1]. *Amblyomma maculatum* is the principal vector of *R. parkeri* infection. Typical symptoms include a necrotic inoculation eschar that occurs several days following the bite of a tick, followed by a low to moderate fever. In 2009, Chen et al. [53] reported a probable case of *R. parkeri* in a 51-year-old traveler returning from Honduras. In 2013, Portillo et al. [54] reported a case of *R. parkeri* infection in which the patient had returned to Spain after a 7-day trip to Southwestern Uruguay.

Indian tick typhus, a tick-borne rickettsiosis prevalent in India, is caused by *Rickettsia conorii indica*. Clinically, the disease resembles MSF; however, a series of three severe cases complicated by gangrene have been recently reported. *R. conorii indica* was isolated from *R. sanguineus* ticks collected in India, although this bacterium has never been isolated in Indian patients. Indian tick typhus also differs from MSF, in that the rash is often purpuric, and an inoculation eschar at the bite site is seldom identified [1]. In 2013, Punj et al. [55] reported a case of *R. conorii* infection with a rapidly evolving petechial rash and digital gangrene in a traveler returning from North India.

3. Flea-borne rickettsioses

3.1. Murine typhus

Murine typhus is caused by *Rickettsia typhi*. The rat flea, *Xenopsylla cheopis*, has been considered as the main vector of this bacterium, and the major causes of human infection are contamination of the respiratory tract or excoriated skin with infected flea feces and more rarely, flea bites. Murine typhus has a worldwide distribution, but the majority of cases are considered to occur in tropical and subtropical regions [56]. Typical clinical manifestations include fever, headache, chills, cough, myalgia, nausea, abdominal pain and hepatomegaly. Rash is not consistent with this infection, as this symptom is often transient or difficult to observe [56—59]. Less common manifestations of murine typhus are lymphadenopathy and splenomegaly. In rare cases, aseptic meningitis, deafness, deep venous thrombosis and retinal manifestations have been reported [5]. Fewer than 50% of patients report exposure to fleas or rats.

In 2004, 50 cases were reported in tourists returning from countries including China, Indonesia, India, Morocco, the Canary Islands, Africa, Malaysia, Southeast Asia, and Thailand, with no deaths [5].

In the past 10 years, approximately 50 more cases of murine typhus have been published, including travelers returning from Asia (23/51, 45%), Africa (33) [57—59], and the Middle East (4%) [60,61], with travelers originating from Europe, Japan, the Canary Islands and Australia. All patients presented with a fever and a flu-like syndrome, and 49% of these individuals had a maculopapular rash (25/51) [56,58,60—66]. In 2010, three cases of *R. typhi* infection were reported in travelers from Tunisia; these individuals were observed during late summer and early autumn, and the patients suffered from persistent fever. However, none of these individuals presented a rash [57]. Severe forms of this disease have been reported, such as acute cholecystitis associated with murine typhus [67] and liver and kidney dysfunction in a Japanese traveler returning from Bali [66]. Progressive pulmonary edema and prolonged fever in a returning traveler from Indonesia were also reported [61]. In 2012, Walter et al. [56] reported 32 confirmed cases of murine typhus in returned travelers. The classic triad of fever, headache, and skin rash was observed in the majority of cases, but two patients presented with life-threatening conditions: one patient presented with septic shock upon admission and the other patient presented with myocarditis. In 2013, two cases of encephalitis were reported. One case involved a 53-year-old man who became ill one week after returning from a two-week holiday to Bali, Indonesia, and the other case involved a 59-year-old female who presented two weeks after returning from Bali with a 1-week illness characterized by myalgia, headache, and fever [60]. In each case, evolution was favorable with doxycycline. No deaths were reported. In most of the cases in ill returned travelers, diagnosis frequently took days, as patients presented with unspecific symptoms. Thus, murine typhus should be tested in any ill returned travelers presenting with "fever of "fever of unknown origin".

4. Louse-borne rickettsioses

4.1. Epidemic typhus

Epidemic typhus is caused by *Rickettsia prowazekii*. The vector of epidemic typhus is the body louse, *Pediculus humanus humanus* (*P. humanus corporis*). Thus, transmission occurs in louse-infested environments, such as refugee camps and prisons and is unlikely to affect the ordinary traveler (for which transmission would occur through the inhalation of louse feces). Most cases of epidemic typhus reported in southeastern U.S.A. have been associated with contact with flying squirrels, suggesting that infection spreads to humans through ectoparasite feces that become aerosolized when the flying squirrels groom themselves [68].

The incubation period of epidemic typhus ranges from 10 to 14 days. Patients develop malaise and vague symptoms before the abrupt onset of symptoms, including fever, headache, and myalgia. Other frequent symptoms include nausea or vomiting, coughing, and abnormalities of the central nervous system function ranging from confusion to stupor to coma. Diarrhea, pulmonary involvement, myocarditis, splenomegaly, and conjunctivitis might also occur. Most patients develop an eruption that classically begins on the trunk and spreads to the limbs, and this disruption might be macular, maculopapular, or petechial and can be difficult, however, to detect on pigmented skin. The gangrene of the distal extremities might occur in severe cases. The case fatality rate in outbreaks was estimated to range from 60% before the availability of antibiotics to 4% in the antibiotic era [68]. Epidemic typhus has been sporadically reported in international travelers [2].

The recrudescence of epidemic typhus in the form of Brill-Zinsser disease can occur many years after the acute infection without new exposure. This eruption is less frequent, and the disease is generally milder.

In 2004, Jensenius et al. [5] reported two travel-associated cases. The first case involved a 38-year-old female aid worker deployed to Burundi and admitted to the hospital with fever and constitutional symptoms at three days after returning to Switzerland. The patient received a tentative diagnosis of viral hemorrhagic fever or typhoid fever and did not receive tetracycline. The patient died of multi-organ failure four days later. The second patient, a 65-year-old male traveler to rural Algeria, developed disseminated intravascular coagulation and acute renal failure after returning to France, but rapidly improved during treatment with intravenous tetracycline [5].

In 2012, Faucher et al. [69] reported a case of Brill-Zinsser disease in a 69-year-old Moroccan man living in France whose last trip to Morocco occurred 4 years ago. After 2 days of high-grade fever associated with headache, myalgia, fatigue, and mild cough, amoxicillin was prescribed for a putative diagnosis of acute respiratory infection. The patient was admitted 2 days later to the hospital for persistent fever. Stupor developed at two days post-hospitalization. The cerebrospinal fluid test results were normal. Because the patient lived near a goat farm, Q fever and tularemia were considered plausible hypotheses, and oral doxycycline was introduced. The patient became afebrile after 48 h and was discharged from the hospital and remained well. On the basis of serologic analysis through Western blotting, *R. prowazekii* infection was finally confirmed in this patient, who had no recent travel and no contact with lice [69]. It was quite impossible to suspect this diagnosis clinically, but testing rickettsioses is dramatically important in patients with a fever of unknown origin, particularly returning travelers.

5. Scrub typhus

Scrub typhus is one of the most common infectious diseases of rural south and southeastern Asia. This disease is an acute febrile illness caused by *O. tsutsugamushi* following the bite of infected mite vectors. The transmission of this etiologic agent to the rodent host or the human incidental host occurs during feeding of the parasitic larval or "chigger" stage of mites, primarily of the genus *Leptotrombidium* [70].

The clinical course includes fever and generalized lymphadenitis, a macular rash and an eschar. Many cases

Table 4 Scrub Typhus: countries of exposure and clinic characteristics.

Authors	Patients, age	Visited countries	Eschar	Complications
Seilmaier et al. [73]	German man, 49	Vietnam Myanmar Thailand	Yes	No
Jensenius et al. [74]	Swedish man	Thailand	Yes	No
	Swedish man	Laos	Yes	No
	Swedish man	Sri Lanka	Yes	No
Nachega et al. [75]	Belgian man, 51	India	Yes	Prostration, trigeminal neuralgia
Matsumura et al. [79]	Japanese man, 49	Myanmar	Yes	Rhabdomyolysis, pneumonia, Enteritis
Izzard et al. [71]	Australian woman	Dubai	Yes	No
Keller et al. [79]	German boy	Thailand	No	No
Vliegenthart — Jongbloed et al. [72]	Dutch woman	India	Yes	No
	Dutch man	India	No	No
Edouard et al. [78]	English woman	Vietnam	Yes	Pneumonia
Henry et al. [76]	English man, 56	India	No	Multi organ system failure
Total	Sex ratio 3	Asia 92%	75%	33%

are mild, but if left untreated, pneumonitis, meningoencephalitis, disseminated intravascular coagulation, or renal failure is commonly observed. The case fatality rate has been estimated as approximately 10%, unless treated appropriately [70].

Jensenius et al. [5] reported more than 20 cases of travel-associated scrub typhus from Europe, North America, and Japan between 1980 and 2004, with two cases of multi-organ system failure in a 51-year-old U.S. man and a 32-year-old French woman. Since that review, 10 additional cases of travel-associated scrub typhus have been published (Table 4). All travelers returned from Asia (Vietnam, Myanmar, Thailand, Laos, Sri Lanka, and India), except for one individual who returned from Dubai [71]. These individuals primarily originated from Europe [72—78], but two travelers were from Australia and Japan [71,79]. All of the infected individuals presented a maculopapular rash, and all but one individual (8%) had an eschar. Most cases were typical, but severe forms were reported for three cases (25%). One such case involved a 51-year-old Belgian traveler returning from a month-long backpacking excursion in southern India. High fever developed abruptly at 7 days before consulting, associated with severe myalgia, dry cough, a disseminated maculopapular rash with confluent vasculitic lesions on both legs, and sensitive enlarged lymph nodes in the cervical and axillary areas; an eschar was observed on the left axilla. During hospitalization, this individual presented prostration and left-sided trigeminal neuralgia for a few weeks, but evolution was favorable with doxycycline [75]. The second case involved a Japanese 49-year-old man who had presented with persistent fever, headache, and rash after a 12-day forest inventory in Myanmar. Upon admission, this patient had a generalized maculopapular rash but no apparent eschars characteristic of scrub typhus. On the ninth day, the patient deteriorated and suffered complications of rhabdomyolysis, pneumonia, and enteritis. Based on a tentative diagnosis of typhoid fever or rickettsiosis, we administered ceftriaxone and minocycline, which dramatically reduced clinical signs and symptoms. Additionally, serology for scrub typhus was positive in the convalescent phase [79]. The third case of scrub typhus occurred in a traveler returning from a trip to India, presenting with multiple organ failure and septic shock [76]. In December 2013, a case of scrub typhus was diagnosed in our laboratory, in a 50-year-old woman returning from a trip to Thailand and Laos. The patient consulted in Lyon, France for febrile rash with an eschar and rapidly presented respiratory distress requiring intensive care. The infection was diagnosed through serology and positive PCR from a skin swab. Evolution was favorable after doxycycline treatment.

6. Ehrlichiosis and anaplasmosis

Ehrlichia chaffeensis is the etiologic agent of human monocytotropic ehrlichiosis (HME). This emerging zoonosis causes clinical manifestations ranging from a mild febrile illness to a fulminant disease characterized by multi-organ system failure. The primary tick vector of HME is *Amblyomma americanum* [80]. In 2013, according to GeoSentinel, a single case of HME related to travel has been listed. This case involved a 32-year-old woman, but clinical and epidemiological details were not described [3].

Human granulocytic anaplasmosis (HGA) is attributable to *Anaplasma phagocytophilum* and is transmitted through *Ixodes* ticks [80]. Since the first case reported in the United States in 1990, HGA has also been described in Europe and Asia. HGA presents as a nonspecific febrile illness, with headache, malaise, and myalgia; less common signs include nausea, abdominal pain, diarrhea, and cough. Although the fatality rate is $<1\%$, various complications, such as septic shock or toxic shock-like syndrome, respiratory insufficiency, rhabdomyolysis, pancarditis, acute renal failure, and hemorrhage, can occur several days or longer after onset [81].

In 2009, Jensenius et al. [7] published an uncomplicated case of human granulocytic anaplasmosis in a 32-year-old U.S. female tourist to the Netherlands. In 2007, Peris-Garcia et al. [82] reported the case of a 57-year-old woman who had a high fever, headaches and joint pain for four days. The woman originated from the Czech Republic

and traveled to Spain for one week. The patient noted a tick bite 15 days earlier, but no skin lesions were observed in the examination. The patient was successfully treated with doxycycline.

7. Acute Q fever

Q fever is a zoonosis caused by *C. burnetii*, a prevalent pathogen observed worldwide, but is absent in New Zealand and French Polynesia. Routes of transmission include the inhalation of contaminated aerosols from amniotic fluid, placenta or wool and the consumption of raw milk; other rare routes of transmission include tick-bites, person-to-person or sexual transmission [83].

The incubation period has been estimated as approximately 20 days (range, 14—39 days). There is no typical form of acute Q fever, and the clinical signs vary greatly between individual patients. The most frequent clinical manifestation of acute Q fever is a self-limited febrile illness associated with severe headaches, myalgia, arthralgias and cough. Other common symptoms of Q fever include pulmonary signs and elevated liver enzyme levels, which can be isolated or coexisting [83]. All acute infections, including asymptomatic infections, can subsequently generate endocarditis or a vascular infection. The definition, diagnosis and treatment of Q fever endocarditis, vascular infection and other localized diseases has been recently reviewed [83,84]; thus, these issues have not been discussed in this work.

Since 1990, nearly 250 cases of travel-acquired acute Q fever have been described [85—97]. In particular, cases have been reported for soldiers deployed during the conflicts in Bosnia, Iraq and Afghanistan. The main obstacle in the diagnosis of Q fever is the lack of specific symptoms. Four cases were published for French soldiers returning from Bosnia [85]. These individuals presented a flu-like syndrome in all cases and pneumonia in a single case. The symptoms occurred at 15 days after time in a bivouac in a sheepfold [85]. In Afghanistan, 26 undifferentiated fevers were observed at the British field hospital in Helmand over the course of only five months (from May to October 2008). Six cases (26%) were acute Q fever, and five cases (22%) were rickettsial infections (unspecified) [86]. Several reports from Iraq have described a higher number of cases of Q fever in U.S. soldiers than expected, and clinicians should have a high index of clinical suspicion and knowledge of diagnostic tests [87]. Approximately 59 cases in U.S. soldiers returning from Iraq have been published [87—91]. Interestingly, in 2010, the sexual transmission of Q fever between a U.S. soldier returning from Iraq and his wife was suspected based on symptoms presented by the wife [89]. Moreover, in 2013, an unusual case of acalculous cholecystitis and Guillain-Barré syndrome, in which the patient was subsequently observed to have acute Q fever, was reported for a 44-year-old civilian security officer medically evacuated from Iraq [91].

Acute Q fever has also been described in tourists [34,85,92—97]. In most cases, the symptoms were nonspecific without complications. These individuals acquired the disease in Lebanon, French Guyana, the Reunion Islands, the Comoros Islands, Gambia, Mozambique, Kenya, the Ivory Coast, Burkina Faso, Sudan, the Saharan Desert, Venezuela, the Dominican Republic, the Philippines, Sri Lanka, and Australia [34,85,92—97]. A case of coinfection of Q fever and malaria was reported for a 29-year-old woman returning from the Comoros Islands. This patient was hospitalized with fever, headache, vomiting and myalgia, which occurred at three days after returning from a four-week trip. The woman did not take any malaria prophylaxis and reported contact with cats and goats and the consumption of unpasteurized dairy products during her stay. Upon examination, the patient presented with a fever and moderate jaundice. Laboratory analysis indicated a parasitemia of 1% with *Plasmodium falciparum*, and the Q fever serological results were positive [93].

8. How to diagnose rickettsioses and Q fever in travelers

Epidemiological and clinical data guide the diagnosis of rickettsioses in many cases. Rickettsial diseases in returnees from a trip are typically suspected based on clinical symptoms, which include fever, headache, myalgia, rash, local lymphadenopathy, and a characteristic inoculation eschar at the bite site for the SFG rickettsioses and scrub typhus. However, typical signs might be absent or unnoticed in an undirected clinical examination. An isolated fever without accompanying signs can be a rickettsiosis, and the diagnosis should be discussed. Currently, isolated and undiagnosed fevers represent 40% of the fevers diagnosed upon return from travel [3].

New approaches for common nonspecific laboratory methods and specific methods for the diagnosis of rickettsioses were reviewed in 2013 [1]. These methods include serology, cultures, histochemical and immunohistochemical methods and molecular tools available in recent years. Serological tests are the easiest, and most frequently used and widely available method for the diagnosis of rickettsioses and Q fever. However, seroconversion is typically detected 7—15 days after the onset of disease. For rickettsioses, most commercially available micro-immunofluorescence (MIF) assays and national reference centers offer a limited selection of antigens that cross-react with different rickettsiae. Therefore, MIF might be adequate for the diagnosis of rickettsioses but not for the definitive identification of the etiologic agent or early disease. More sophisticated serological assays can be used to differentiate rickettsial infections, but these methods have only recently become available at few reference centers [1].

In cell culture, rickettsiae might be detectable as early as 48—72 h post-inoculation. To be suitable for culture, the samples must be collected prior to the initiation of an antibiotic regimen and as early as possible in the course of the disease. However, culturing is less available than serology and quantitative PCR (qPCR) for the diagnosis of rickettsiosis [1].

A new method for the diagnosis of rickettsioses has been recently achieved with the emerging use of quantitative real-time PCR. Quantitative PCR can be performed from a blood sample, skin biopsy, eschar crust or swab (Fig. 5), or when an eschar is present (in SFG rickettsiosis or scrub

typhus). In 2012, the usefulness of eschar swabs and/or eschar crust samples was reported for the diagnosis of *R. africae* infection in returning travelers [38]. At the WHO collaborative center FRA 75 for rickettsioses and other arthropod-borne bacterial diseases, in Marseille, France, we regularly receive eschar swabs through mail from Africa and Europe, facilitating rapid diagnosis using molecular tools (procedure on request) [1].

Travelers can also collect the biting ticks and bring them to a physician to assess the risk of infection. The identity of the tick species can be obtained through several methods, including classic entomological identification. However, the morphological identification of a tick requires entomological expertise and specific documentation. Typically, many physicians examining a patient with an attached or removed tick will not know the few places in their country where tick can be identified and how useful this information could be [98]. New tools for tick and other arthropod identification have been recently developed, including molecular tools or matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) [99]. MALDI-TOF MS might be a revolutionary technique for the future, as the results were obtained rapidly relative to the time required for molecular methods, and the completion of this assay did not require any specific entomological expertise. At the WHO Collaborative Center for Rickettsioses and Other Arthropod Borne Bacterial Diseases, Marseille, France, we have created a database that is regularly updated through the addition of new reference spectra to quickly identify ticks [99]. If a tick is a recognized vector for a specific disease, then this information can inform physicians regarding which specific clinical signs they should look for in patients. Ticks can also be used as indirect diagnostic tools through the detection of potential agents using currently developed molecular tools and the future use of MALDI TOF [99] .

Figure 5 Use of skin eschar swabs for the diagnosis of tick-borne rickettsioses through qPCR analysis.

9. Treatments

When typical signs are encountered (such as a rash and inoculation eschar(s), suggesting a spotted fever group rickettsiosis or scrub typhus), treatment should be initiated prior to laboratory confirmation of the diagnosis [100].

Doxycycline remains the standard treatment for all spotted fever group rickettsioses. This treatment has been associated with better outcomes than other regimens [100]. Doxycycline is also recommended as a first choice in children, as no staining of teeth and good tolerance during short-term treatment has been reported [101,102]. Fluoroquinolones have been presented as an alternative to doxycycline, but recent studies have shown that these compounds are associated with a deleterious outcome during *R. conorii* infection in humans and in a cell culture model, potentially reflecting the up-regulation of a toxin-antitoxin module [100]. Macrolides, such as josamycin, clarithromycin and azithromycin, might represent alternatives for the treatment of some rickettsioses, particularly in pregnant women. Corticosteroid therapy has not proven effective [100].

Doxycycline has a proven efficacy in scrub typhus, although resistance has been documented in parts of northern Thailand. The outcomes of drug treatments in Asian patients with scrub typhus showed no significant differences between macrolides (azithromycin) and doxycycline treatments for the duration of fever, rapidness of symptom clearance, or rate of treatment failure. Azithromycin (including a single 500-mg dose) can be used during pregnancy and in children [103]. Chloramphenicol may be used during pregnancy [104]. Rifampicin is effective in areas where doxycycline resistance has been described or in areas where the response to standard anti rickettsial drugs is poor. Quinolones have shown some degree of efficacy in scrub typhus, but this evidence is limited. The optimal duration of therapy is uncertain. However, the short courses of treatment (doxycycline or chloramphenicol) have been associated with an increased risk of relapse, and no relapses were observed in patients treated with either regimen for five days or longer.

The treatment of murine typhus and epidemic typhus is 100 mg of Doxycycline, administered twice a day and continued 3 days after healing.

The treatment for acute Q fever is 100 mg of Doxycycline, administered twice a day for 14—21 days. Fluoroquinolones, macrolides such as erythromycin, clarithromycin and roxithromycin, are considered to be a reliable alternative to treat acute Q fever. Cotrimoxazole is recommended until delivery in pregnant women diagnosed with acute Q fever (83).

As previously described, when no diagnosis is evident for an ill returned traveler, all rickettsioses and Q fever must be considered. When diagnostic tools are not available or when the results will be delayed, the use of empirical doxycycline treatment should be discussed, particularly when empirical treatment with beta-lactams has failed or under severe conditions.

10. How to protect travelers

The best way to protect travelers against most rickettsial diseases is to prevent vector bites. Wearing long trousers

tucked into boots and using tick repellents are effective tools for reducing the risk of tick bites and pathogen transmission [105,106]. The best method to avoid tick (and many other arthropod) bites has 2 components: the topical application of 10—35% DEET (*N*,*N*-diethyl-*m*-toluamide) or EBAAP (ethyl-butylacetylaminopropionate) repellent to exposed skin and the treatment of clothing with permethrin. DEET used directly on exposed skin only repels ticks, thus providing little protection, however permethrin (treatment of clothing) kills ticks on contact. Some repellents provide up to 12 h of protection with one application, and long-acting formulations are currently being developed [105—108]. In all cases, the observed ticks should be immediately removed. Rickettsiae are usually observed in the salivary glands and can be transmitted before the beginning of meal; thus, attached ticks should be removed as soon as possible, as the risk of infection is only slight in the first 6 h after the tick bite.

Avoiding the consumption of unpasteurized dairy products might reduce exposure to food contaminated with Q fever. Unfortunately, nothing can protect against infection through aerosol.

Interestingly, it is not known whether doxycycline regimen prescribed for malaria prophylaxis would be effective in preventing rickettsioses. The effectiveness of the prophylactic administration of doxycycline in the prevention of scrub typhus has been demonstrated in two prospective randomized double blind studies. The first study included a total of 1125 military subjects who were followed for periods as long as five months of exposure in a hyperendemic focus in the Pescadores Islands of Taiwan. Oral 200-mg doses of doxycycline or placebo were administered once each week throughout the trial (notably, this treatment is not the typical dose of malaria prophylaxis). The incidence rate of scrub typhus in the placebo group was 2.5 times greater than that for the group receiving doxycycline. When subjects who failed to comply with the scheduled administration of doxycycline were removed from the analysis, the incidence rate of scrub typhus in the control group was five times greater than that in the drug group [109]. The second study involved the observation of twenty volunteers at three days prior to exposure to *Leptotrombidium* chiggers infected with *O. tsutsugamushi* and continued for six weeks after exposure. One group received weekly 200-mg oral doses of doxycycline (notably, this treatment is not the typical dose of malaria prophylaxis), and the other group received a placebo. Nine of 10 doxycycline-treated subjects remained healthy during prophylaxis, but developed antibodies to scrub typhus, whereas nine of the 10 subjects given the placebo required treatment for scrub typhus. Therefore, the efficacy of the regimen in preventing scrub typhus was 89% [110].

Moreover, in 2013, Mediannikov et al. [111] suggested that doxycycline should be used as a first choice for chemoprophylaxis against malaria in travelers to sub-Saharan Africa to protect against rickettsioses. Indeed, these authors reported a common epidemiology of malaria and *Rickettsia felis* infection in sub-Saharan Africa [111]. *R. felis* is an emerging pathogen transmitted through fleas [112] and might also be associated with other arthropods, including mosquitoes (the same methods used for other rickettsial diseases were used to diagnose *R. felis* infection). Although few cases have been reported, *R. felis* is now known to be a significant cause of fever of unknown origin in sub-Saharan Africa [111].

11. Conclusion

With more than 500 reported cases of rickettsial diseases and acute Q fever in travelers since 2004, rickettsial

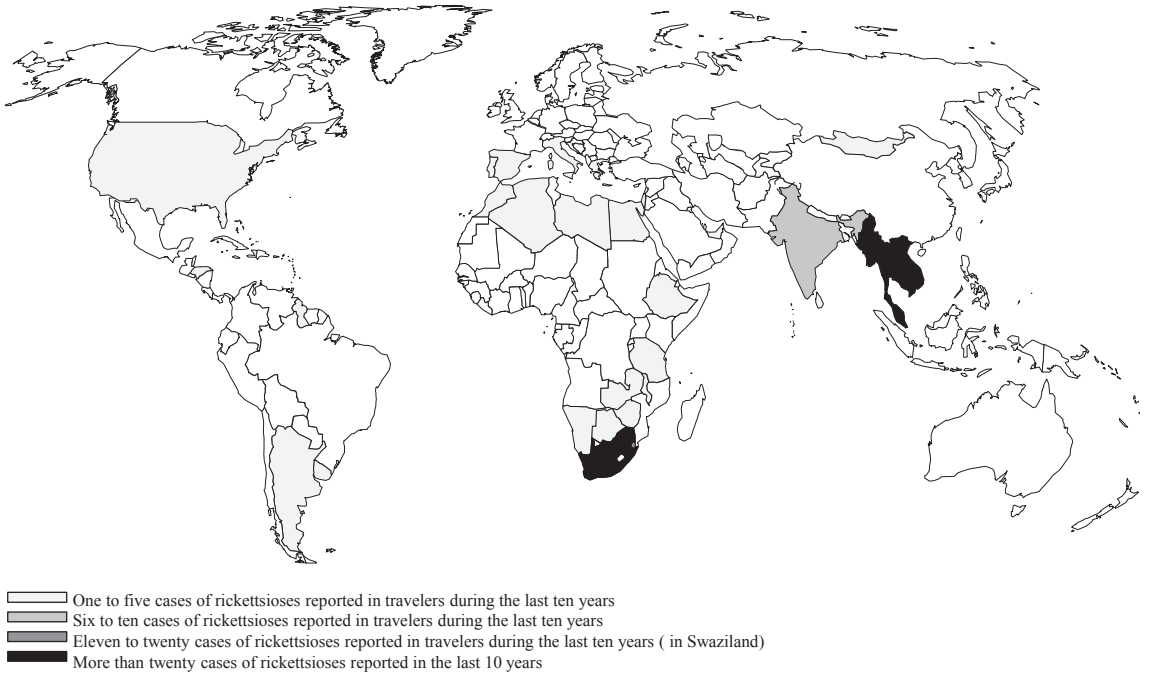

Figure 6 Repartition of cases of imported rickettsioses in travelers during the last ten years.

diseases are emerging pathologies that must be identified in ill returning travelers, although these diseases remain unknown to many practitioners. Travelers might be infected worldwide, however the risk depends on the geography of travel and the activities undertaken (Fig. 6). ATBF occurs more frequently than typhoid or dengue [113] in travelers returning from sub-Saharan Africa.

Occasionally, typical clinical signs, such as rash and eschar for spotted fevers, are observed. However, these symptoms must be carefully detected, and immediate doxycycline treatment is required pending laboratory results. New molecular diagnostic methods have been recently described [1], in particular those involving samples obtained from eschar swabs, which might easily be used at the bedside or during outpatient consultations, and the samples can subsequently be sent to laboratories with PCR facilities. These methods not only confirm diagnosis but also identify the species involved and might contribute to the description of new diseases.

However, many diseases might present with some unspecific signs, such as murine typhus or Q fever and even tick-borne spotted fever. "Fever of unknown origin" in travelers after a trip is common [6]. When no diagnosis is evident, rickettsioses must be considered, at least through serological assays. When diagnostic tools are not available or when the results will be delayed, the use of empirical doxycycline treatment should be considered, particularly when empirical treatment with beta-lactams has failed. Furthermore, although it will be difficult to implement evidence-based guidelines, we suggest that chemoprophylaxis using doxycycline for malaria prevention in travelers will be effective against most rickettsioses.

Conflict of interest

None.

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