Rickettsioses and the International Traveler

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The rickettsioses—zoonotic bacterial infections transmitted to humans by arthropods—were for many years considered to be oddities in travel medicine. During the previous 2 decades, however, reports of >450 travel-associated cases have been published worldwide, the vast majority being murine typhus caused by *Rickettsia typhi,* Mediterranean spotted fever caused by *Rickettsia conorii,* African tick bite fever caused by *Rickettsia africae,* and scrub typhus caused by *Orientia tsutsugamushi.* Most patients present with a benign febrile illness accompanied by headache, myalgia, and cutaneous eruptions, but severe complications and fatalities are occasionally seen. Current microbiological tests include culture, polymerase chain reaction, and serological analysis, of which only the latter method is widely available. Tetracyclines are the drugs of first choice and should be prescribed whenever a case of rickettsiosis is suspected. Preventive measures rely on minimizing the risk of arthropod bites when traveling in areas of endemicity.

Rickettsioses are acute febrile, zoonotic diseases caused by rickettsiae, which are obligate intracellular Gram-negative bacteria that invade endothelial cells and induce the formation of vasculitis. Various arthropods, including lice, fleas, ticks, and mites, can act as vectors, whereas mammals and sometimes the arthropods themselves constitute the principal reservoirs [1]. Eighteen rickettsioses, divided into 3 biogroups, are currently recognized: 2 diseases are in the typhus biogroup, 15 are in the spotted fever biogroup, and 1 is in the scrub typhus biogroup (table 1).

Rickettsioses were for many years considered to be oddities in travel medicine. However, since 1988, when the first comprehensive series of travel-associated rickettsioses was published [2], >450 cases have been reported in the literature. This increase is likely attributable to improvements in diagnostic awareness and the availability of microbiological tests, as well as to increases in travel to areas of endemicity and in risk behavior (e.g., backpacking and ecotourism) among travelers. In this article, we describe the epidemiology and clinical presentation of the rickettsioses currently encountered in travel medicine and outline the current status of microbiological diagnosis, treatment, and prevention.

MURINE TYPHUS

Murine typhus is caused by *Rickettsia typhi,* a rickettsia species in the typhus biogroup. Rats and other rodents act as reservoirs, and the Asiatic rat flea *Xenopsylla cheopis* is the principal vector. Humans are infected by inoculation of infective flea feces in bite wounds. Murine typhus is widely distributed in tropical and subtropical areas, particularly in port cities and costal regions with rodents. The clinical presentation is notoriously nonspecific, with fever, constitutional symptoms, and an often poorly visible maculopapular exanthema on the trunk as its main features. As a result, murine typhus is frequently misdiagnosed, and its incidence may be grossly underestimated. Most cases are mild, but the fatality rate may be as high as 4% [3].

Murine typhus has been reported in ~50 travelers returning from Asia (Nepal, India, Thailand, Indonesia, China, and Vietnam), Africa (Morocco, Gabon, Botswana, and Guinea Bissau), and Europe (Cyprus, Greece, and Spain) [2, 4–8]. Many patients reported previous travel to port cities or beach resorts (figure 1), and some can even recall direct contact with rats. Some infected travelers, however, have not visited typical areas of endemicity and may actually have "murine typhus–like rickettsiosis" caused by *Rickettsia felis,* a spotted fever group rickettsia transmitted by cat fleas and usually associated with felines [9]. Usually, murine typhus is a benign disease in travelers, but aseptic meningitis, deafness, deep venous thrombosis, and even death have been reported [5].

MEDITERRANEAN SPOTTED FEVER

Mediterranean spotted fever and its variants—Astrakhan fever, Israeli tick typhus, and Indian tick typhus—are caused by *Rickettsia conorii* and transmitted by dog ticks in urban and suburban areas. The disease is present in Europe, Africa, and Asia, with the principal foci comprising the Mediterranean and Caspian littorals. Typical clinical features include fever, constitutional symptoms, a generalized maculopapular cutaneous rash, and an inoculation eschar at the site of the tick bite. Most cases are mild, but complications are not uncommon and include neurological involvements, peripheral gangrene, and respiratory distress syndrome. The overall fatality rate is ∼2% [10].

Mediterranean spotted fever has been reported in >35 travelers from northern Europe and North America. The majority of individuals are infected in the Mediterranean area, including popular tourist destinations in southern France and Spain [2, 4, 6, 8, 11–16]. Case histories typically include physical contact with local dogs [16]. Most travel-associated cases of Mediterranean spotted fever are mild and uncomplicated, but visual loss was reported in a British traveler who returned from Africa [12], and a 39-year-old US missionary deployed to Kenya died of multiorgan failure despite prompt medical attention at a local hospital [17].

AFRICAN TICK BITE FEVER

African tick bite fever is caused by *Rickettsia africae* and is endemic in large parts of rural sub-Saharan Africa and the eastern Caribbean (figure 2). In a recent study from Cameroon, 32% of 234 patients presenting with acute pyrexia not caused by malaria or typhoid fever had serological evidence of acute *R. africae* infection. [18]. Cattle ticks of the *Amblyomma* genus act as both reservoirs and vectors, and indigenous cases are typically acquired during agricultural work. The implicated ticks are locally very common on the vegetation (especially during the rainy season), are notoriously aggressive, and readily bite humans. The clinical presentation includes headache, neck myalgia, and one or several inoculation eschars with regional lymphadenitis (figure 3), whereas a vesicular cutaneous rash and mouth blisters are seen in up to 30% of the patients. African tick bite fever is usually a self-limited, mild disease, and no fatalities have been reported to date [19].

With >350 imported cases reported from Europe, North and South America, Asia, and Oceania during the past few years, African tick bite fever is without comparison currently the most commonly encountered rickettsiosis in travel medicine [20]. Most patients are infected during wild game safaris and bush walks, often of surprisingly short duration. African tick bite fever

Table 1. Current classification of rickettsioses and their estimated incidence among international travelers.

Biogroup, disease	Species	Principal vectors	Geographic distribution	Incidence among travelers to areas of endemicity
Typhus				
Epidemic typhus	*Rickettsia prowazekii*	Body lice	Central Africa, South America	Very rare
Murine typhus	*Rickettsia typhi*	Rat fleas	Tropical and subtropical areas worldwide	Occasional
Spotted fever				
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor* and *Amblyomma* ticks	North and South America	Very rare
Mediterranean spotted fever[a]	*Rickettsia conorii*	*Rhipicephalus* and *Haemaphysalis* ticks	Mediterranean and Caspian littorals, Middle East, Indian subcontinent, Africa	Occasional
Siberian tick typhus	*Rickettsia sibirica*	*Dermacentor* ticks	Northern Asia	Very rare
Unnamed	*Rickettsia sibirica mongolotimonae*	*Hyalomma* ticks	China, France, sub-Saharan Africa	No data
Queensland tick typhus	*Rickettsia australis*	*Ixodes* ticks	Eastern Australia	Very rare
Flinders Island spotted fever	*Rickettsia honei*	Ticks of several genera	Australia, Southeast Asia, northwestern North America	No data
African tick bite fever	*Rickettsia africae*	*Amblyomma* ticks	Sub-Saharan Africa, Caribbean	Common
Japanese spotted fever	*Rickettsia japonica*	Ticks of several genera	Japan	No data
Rickettsialpox	*Rickettsia akari*	Mouse mites	North and South America, Asia	No data
California flea rickettsiosis	*Rickettsia felis*	Cat fleas	Europe, North and South America, Africa, Asia	No data
Unnamed	*Rickettsia heilongjiangensis*	*Dermacentor* ticks	Eastern Asia	No data
Unnamed	*Rickettsia slovaca*	*Dermacentor* ticks	Southern and eastern Europe	No data
Unnamed	*Rickettsia helvetica*	*Ixodes* ticks	Central and northern Europe, Asia	No data
Unnamed	*Rickettsia aeschlimannii*	*Hyalomma* ticks	Mediterranean littoral, Morocco, South Africa	Very rare
Unnamed	*Rickettsia parkeri*	*Amblyomma* ticks	United States	No data
Scrub typhus, scrub typhus	*Orientia tsutsugamushi*	Chigger mites	Southeast Asia, western Oceania	Occasional

[a] Including Astrakhan fever, Israeli tick typhus, and Indian tick typhus.

Figure 1. A road with litter (and rodents) in a Mediterranean holiday resort—a typical area of murine typhus endemicity

frequently occurs in clusters—an important epidemiological feature—and may sometimes present as large and spectacular outbreaks among safari tourists, military personnel, game hunters, sports participants, or school students [19, 21, 22]. The incidence of African tick bite fever among short-term safari tourists may be impressive (4%–5.3%) and widely exceeds those reported for other tropical fevers among short-term visitors to sub-Saharan Africa. Identified risk factors include game hunting, travel during the summer season, and travel to southern Africa, where the

incidence of African tick bite fever appears to be particular high. Reactive arthritis may complicate 5% of travel-associated cases [23], and some patients may develop subacute cranial or peripheral neuropathy (M. Jensenius et al., unpublished data).

SCRUB TYPHUS

Scrub typhus is one of the most common infectious diseases of rural south and southeastern Asia and the western Pacific,
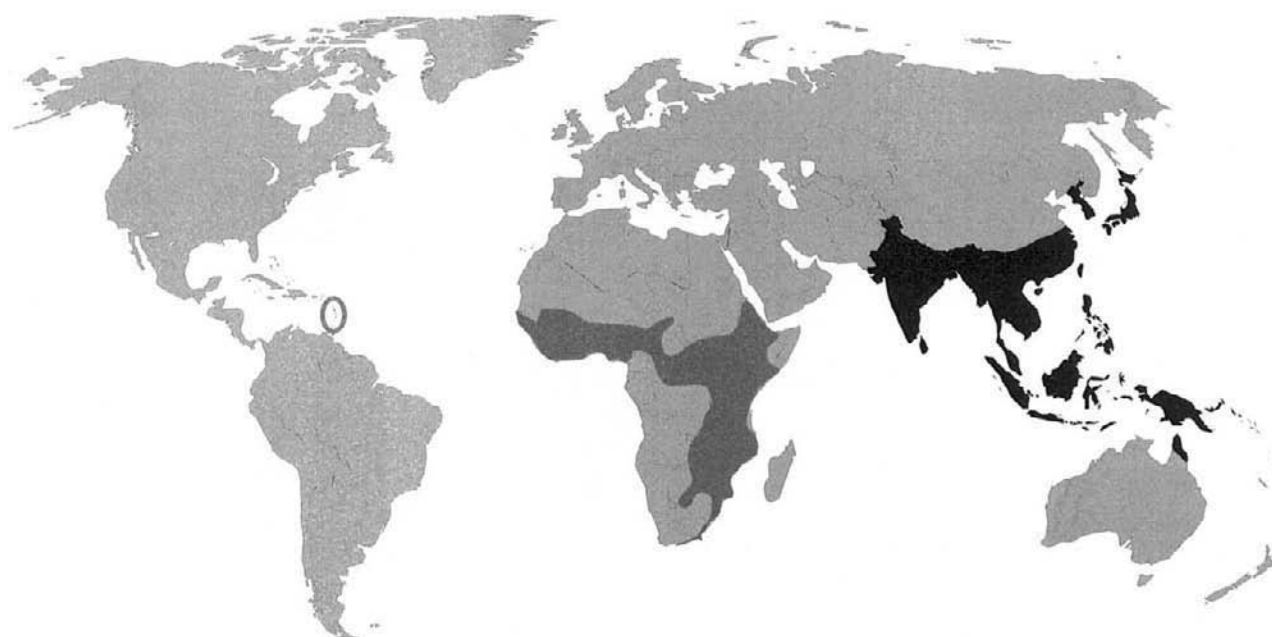

Figure 2. Distribution of African tick bite fever in Africa and eastern Caribbean *(dark grey)* and of scrub typhus in Asia and Oceania *(black)*

Figure 3. Multiple inoculation eschars in a male traveler with African tick bite fever

where an estimated 1 million cases occur each year, mainly among humans engaged in logging, clearing of land, and working in rice fields (figure 2). Military personnel are also at risk, and scrub typhus had a significant impact on troops during World War II and the Vietnam War. The disease is caused by *Orientia tsutsugamushi,* which is transmitted by the bites of larval trombiculid mites (chiggers). The larvae typically bite humans on the lower extremities or in the genital region (where they may be difficult to recognize). More than 80% of patients present with fever and a generalized lymphadenitis, and 50% have an inoculation eschar. Many cases are mild, but if left untreated, pneumonitis, meningoencephalitis, disseminated intravascular coagulation, or renal failure are commonly seen. The fatality rate of scrub typhus ranges from 1%–35%, depending on the virulence of the infecting strain, host factors, and treatment [24].

Since 1986, ~20 cases of travel-associated scrub typhus have been reported from Europe, North America, and Japan [2, 4, 6, 24–27]. Most patients are infected in Thailand, but some are infected in India, Burma, Vietnam, Malaysia, Papua New Guinea, The Philippines, and Korea. Typical itineraries include visits to rural areas that involve camping, trekking, or rafting (figure 4). Complications are rarely reported in travelers, but life-threatening multiorgan failure was seen in a 51-year-old US man infected in Thailand [25] and in a 32-year-old French female traveler to Burma and Thailand [27].

OTHER RICKETTSIOSES

In addition to the 4 diseases discussed above, another 5 rickettsioses have been sporadically reported in international travelers. Common features for these rarely reported diseases include one or several of the following: their areas of endemicity are restricted to remote settings or to extreme biotopes infre-

Figure 4. Typical area of scrub typhus endemicity in Thailand

quently visited by travelers, the implicated vectors have a low affinity for humans, or only a small minority (typically <1%) of the arthropods in areas of endemicity are infected.

Epidemic typhus caused by *Rickettsia prowazekii* (historically one of the most feared infectious diseases worldwide) is transmitted in louse-infested environments, such as refugee camps and prisons, and is unlikely to affect the ordinary traveler. Two travel-associated cases, however, were recently reported. A 38-year-old female aid worker deployed to Burundi was admitted to the hospital with fever and constitutional symptoms 3 days after returning to Switzerland. The patient received a tentative diagnosis of viral hemorrhagic fever or typhoid fever and did not receive tetracyclines, and she died of multiorgan failure 4 days later [28]. 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 doxycycline [29].

Rocky Mountain spotted fever, another potentially severe rickettsiosis, is caused by *Rickettsia rickettsii* and is transmitted in rural areas by *Amblyomma* and *Dermacentor* ticks. The disease is endemic in the southeastern and midwestern United States and in parts of South America and affects those who have exposure to tick-infested habitats, such as wooded and grassy areas. Rocky Mountain spotted fever has only been reported in a handful of international travelers, who were typically infected during camping or hiking [16].

North Asian tick typhus is caused by *Rickettsia sibirica* and is endemic in rural northern Asia. The disease was recently reported on the basis of results of nonspecific serological analysis in a British volunteer in Mongolia and in 4 US paleontologists deployed to the Gobi desert. All 5 travelers had mild disease, and all recovered uneventfully [30, 31].

Finally, a case of severe Queensland tick typhus caused by *Rickettsia australis* was seen in a 16-year-old visitor to a crocodile farm in Eastern Australia, and an uncomplicated case of *Rickettsia aeschlimannii* infection was reported in a 36-year-old traveler to Morocco [32].

DIAGNOSIS

Three main microbiological diagnostic options are currently available in rickettsiology: culture, PCR, and serological analysis [33]. Isolation attempts on cell cultures may be performed using buffy coat or tissue samples, the latter preferably having been obtained during skin or eschar biopsy. If not processed within 24 h, samples must be frozen at $-70°C$ or in liquid nitrogen. Culture is cumbersome and potentially hazardous and should be reserved for unusual or severe cases in which a specific species diagnosis is considered to be of significant importance.

Blood and tissue samples may also be submitted for PCR, a sensitive, specific, and rapid diagnostic test. Primer sets tar-geting various rickettsial genes, including those encoding 16S DNA, outer membrane proteins, and "gene *D*," have been described and can be used in any laboratory with suitable facilities [34]. If PCR-based diagnosis is delayed for >24 h, samples should be stored at $-20°C$ or lower.

Serological analysis is the most commonly applied microbiological method in rickettsiology but can usually only provide a retrospective diagnosis. Many tests have been described since the Weil-Felix test was developed 90 years ago, but most lack acceptable sensitivity and specificity. Currently, the immuno-fluorescence assay (IFA), a commercially available and widely used test worldwide, is considered to be the reference serological method. Because of extensive cross-reactions, however, IFA is usually unable to determine the causative agent to the species level. To circumvent this problem, serum samples may be shipped to a reference laboratory for Western blotting in conjunction with cross-adsorption assays [35]. Serum specimens for IFA should be collected early in the course of the disease, with a convalescent-phase sample obtained 2 weeks later. If a 4-fold increase in the antibody titer is not observed during this period (a common phenomenon in cases of African tick bite fever [36]), a third sample, collected 4–6 weeks after onset of symptoms, should be considered. Serum samples can be preserved at $-20°C$ or lower for several months without significant degradation of antibodies.

TREATMENT

Because confirmation of diagnosis is difficult during the acute phase and proper treatment is essential for rapid recovery and prevention of complications, presumptive therapy with antirickettsial drugs is recommended whenever a case of rickettsiosis is suspected. The standard regimen consists of doxycycline, 200 mg daily for 3–14 days, depending on the clinical course. Most patients will improve within the first 24 h after the start of therapy, and a delay in response should call the diagnosis into question. Chloramphenicol and the newer macrolides are probably good alternatives to doxycycline [37], whereas fluoroquinolones may fail clinically despite exhibiting good in vitro activity against most rickettsial species, as has been suggested in cases of travel-associated epidemic typhus and murine typhus [28].

PREVENTION

The best preventive measure against rickettsioses is to avoid typical risk settings when traveling in areas of endemicity. For instance, rodents, dogs, and domestic livestock should not be touched, and bush vegetation likely to be infested with ticks or mites should not be entered. If this is not possible, measures aimed at minimizing the risk of arthropod bites should be taken. Travelers to regions in which rickettsioses are highly endemic, such as scrub bushes in Southeast Asia and game

parks in southern Africa, should be recommended to use protective clothing, preferably impregnated with permethrin or another pyrethroid. Topical repellents should be used on any exposed skin, but because of short-lasting effect against many of the implicated vectors (only 1–2 h for many products [38]), frequent application is recommended. Daily self-checking and removal of ticks and mites during travel should be encouraged.

Weekly 200-mg doses of doxycycline can prevent scrub typhus in military personnel deployed to areas of endemicity [39] and is also likely to be a valuable option for backpackers, trekkers, and other visitors at high risk. Whether chemoprophylaxis can prevent the acquisition of other rickettsioses is uncertain, and safari travelers may contract African tick bite fever despite the concomitant use of tetracycline hydrochloride as malaria prophylaxis [19]. No vaccines against rickettsioses are readily available for travelers.

CONCLUDING REMARKS

Unfortunately, precise data on the incidence of rickettsioses among international travelers are not available. Rickettsioses are usually not notifiable to national surveillance systems, and few prospective cohort studies have been performed [23]. Nevertheless, the >450 cases published during the previous 20 years are likely to indicate a significant health problem at many popular tourist destinations. In Switzerland, rickettsioses are actually considered to be the third most common cause of imported acute tropical fever, surpassed only by malaria and typhoid fever [4]. Moreover, because ecotourism is increasingly popular with international travelers, more cases of imported rickettsioses are likely to be seen in Europe and elsewhere in the years to come. Delay in diagnosis and the common practice of prescribing β-lactams as empirical therapy may result in life-threatening complications or permanent disabilities in some infected travelers [24]. Therefore, physicians in areas of nonendemicity must have a high index of suspicion and consider treatment with tetracyclines whenever a case of rickettsiosis is suspected. A microbiological diagnosis should always be attempted, at least by serological analysis. In patients with unusual cases, including those presenting with severe disease or those returning from areas with no known or only poorly described rickettsial activity, species identification by isolation or PCR should be considered. By establishing precise diagnoses and systematically reporting cases of travel-associated rickettsioses to health care authorities, our epidemiologic and clinical concepts of these fascinating zoonotic diseases are likely to expand and, hopefully, will result in better protection of travelers and improved management of infected patients in the years to come.

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