

# African Tick Bite Fever in Travelers to Rural Sub-Equatorial Africa

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**To estimate the incidence of, identify risk factors for, and describe the clinical presentation of travel-associated African tick bite fever (ATBF), a rapidly emerging disease in travel medicine, we prospectively studied a cohort of 940 travelers to rural sub-Equatorial Africa. Diagnosis was based on suicide polymerase chain reaction and the detection of specific antibodies to *Rickettsia africae* in serum samples by multiple-antigen microimmuno-fluorescence assay, Western blotting, and cross-adsorption assays. Thirty-eight travelers, 4.0% of the cohort and 26.6% of those reporting flulike symptoms, had ATBF diagnosed. More than 80% of the patients had fever, headache, and/or myalgia, whereas specific clinical features such as inoculation eschars, lymphadenitis, cutaneous rash, and aphthous stomatitis were seen in  $\leq 50\%$  of patients. Game hunting, travel to southern Africa, and travel during November through April were found to be independent risk factors. Our study suggests that ATBF is not uncommon in travelers to rural sub-Saharan Africa and that many cases have a nonspecific presentation.**

African tick bite fever (ATBF) is an acute, flulike illness that is frequently accompanied by severe headache, inoculation eschars with regional lymphadenitis, vesicular cutaneous rash, and aphthous stomatitis [1, 2]. ATBF is caused by *Rickettsia africae*, a recently identified spotted fever group (SFG) rickettsia, and is transmitted in rural sub-Saharan Africa by ungulate ticks of the *Amblyomma* genus, mainly *Amblyomma hebraeum* in southern Africa and *Amblyomma variegatum* in West,

central, and East Africa [3]. Recent surveys conducted in areas of endemicity have yielded high prevalence rates [4–6], and *R. africae* is now regarded as the most widely distributed of all SFG rickettsiae known to be pathogenic to humans [7].

Paralleled with the rapid expansion of safari tourism to Africa during the past few years, ATBF has emerged as a common cause of imported fever in many areas where it is not endemic [1]. Most travelers are infected in South Africa, Botswana, and Zimbabwe—countries where many popular wildlife attractions at which *R. africae* infection is highly endemic [8]. It is noteworthy, and in contrast to other SFG rickettsioses, that most cases of ATBF occur in clusters that can affect large groups of exposed travelers, such as soldiers, leisure safari tourists, game hunters, sports competitors, students, and foreign aid workers [1, 9–14].

So far, no prospective studies of ATBF have been published, and many central epidemiological and clinical aspects of this disease still remain unclear. To es-

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estimate the incidence of, identify risk factors for, and describe the spectrum of clinical manifestations in consecutive cases of travel-associated ATBF, we prospectively studied a cohort of Norwegian travelers to rural sub-Equatorial Africa.

## MATERIALS AND METHODS

Nine travel-medicine clinics in Oslo, Akerhus, and Sør-Trøndelag counties, Norway, enrolled travelers in the study from 1 January 1999 through 31 December 2000. Consecutive attendees who planned to travel to rural areas in continental sub-Equatorial Africa (including Kenya and Uganda) were given oral and written information on ATBF and were asked to participate in the study. Attendees who agreed to participate were mailed a 2-page questionnaire on their return to Norway. The questionnaire included queries about the country visited, travel time frames, the purpose of travel, bush walking, limited or no use of personal protection against arthropod bites (protective clothing, permethrine, and skin repellents), observed tick bites or ticks on clothes or skin, the use of primitive accommodation (defined as an overnight stay outdoors, in a tent, and/or in a straw hut), and the presence of any flulike symptoms (fever, myalgia, and headache) commencing no later than 10 days after leaving the rural area. Only travelers who submitted a completed questionnaire and reported travel to rural areas were included in the study.

Travelers with flulike symptoms commencing no later than 10 days after leaving rural areas were also asked to present to any of the study group's infectious diseases specialists within 24 h. The medical evaluation included a physical examination with special reference to inoculation eschars, regional lymphadenopathy, cutaneous rash and aphthous stomatitis, and blood sampling for serological testing and PCR. Antirickettsial chemotherapy was administered to patients with fever. However, the choice of agent, dosing, and duration and other diagnostic procedures (including malaria blood smears, urine tests, and radiography) were left to the subjective opinion of the physician in charge. All patients with clinically suspected ATBF were offered a follow-up visit within 2–4 weeks for further medical evaluation. The acute phase was defined as up to 14 days after symptom onset, and the convalescent phase started on day 15. Informed written consent was obtained from all participants or their parents or guardians. The study protocol was reviewed by the Regional Committee for Ethics and Research, Oslo, Norway.

**Microbiological diagnosis.** The microbiological diagnosis was based on the findings of suicide PCR and the detection of specific antibodies to *R. africae* by multiple-antigen immunofluorescence (MIF), Western blot (WB), and cross-adsorption assay of serum samples. In general, the specificity of

most serological tests for rickettsial infections is hampered by extensive cross-reactions caused by immunogenic cell-wall lipopolysaccharide (LPS) antigens. Each of the serological methods that we used, however, has recently been found to have a specificity of 100% in culture- and PCR-proven cases of ATBF [1].

Suicide PCR was done as described elsewhere [1], using the primer pairs AF1F-AF1R and AF2F-AF2R for 13 patients and the 2 primer pairs polF1 (5'-AAAGATATTGAATGTAACGG-3')-polR1 (5'-GAATATTAGTTCTAATATTC-3') and polF2 (5'-GACGAGATTTTACTATTAATGC-3')-polR2 (5'-CTCGTGATAAAGTTTTTAAGCC-3'), which were designed to amplify a fragment of the *pcnB* gene encoding the poly (A) polymerase, for the remaining patients. All positive PCR products were identified by sequencing and comparison with *R. africae* *ompA* (AF primers) or *pcnB* (pol primers) sequences. MIF was done as reported elsewhere [11], using 7 SFG rickettsial antigens: *R. africae* strain ESF-5, *Rickettsia conorii* strain 7 (Malish) ATCC (American Type Culture Collection) VR-613T, *Rickettsia mongolotimonae* strain HA-91T, *Rickettsia aeschlimannii* strain MC16T, *Rickettsia massiliae* strain Mtu1T, *Rickettsia akari* strain MK ATCC VR-148T, and *Rickettsia felis* strain URRWXC2. WB procedures were done as described elsewhere [15], using 20  $\mu$ L of a 1 mg/mL suspension of *R. africae*, *R. conorii*, or *Rickettsia aeschlimannii* antigen per lane. Cross-adsorption for serological testing was done as described elsewhere [16], using *R. africae* and *R. conorii* antigens. All acute-phase serum samples were examined with suicide PCR, MIF, and WB, and all convalescent-phase serum samples were tested with MIF and WB. Serum samples from one-half of the patients for whom PCR, MIF, and WB indicated SFG rickettsial infection but were unable to identify the causative rickettsial species were randomly selected to undergo cross-adsorption assays.

In accordance with recently proposed criteria [1], we considered definite serological evidence of *R. africae* infection to be (1) MIF titers of  $\geq 1:64$  for IgG and/or  $\geq 1:32$  for IgM, with the IgG+IgM titers being at least 2 dilutions higher than any of the other tested SFG rickettsial antigens; (2) a WB profile that revealed only *R. africae*-specific antibodies; or (3) cross-adsorption assays demonstrating that the homologous antibodies were directed against *R. africae*. For serological evidence of recent nondeterminable SFG rickettsiosis, we accepted MIF titers of IgG of  $\geq 1:64$  and/or titers of IgM of  $\geq 1:32$  that did not fulfill the above criteria or a WB demonstrating antibodies directed against high-molecular-weight surface proteins and LPS antigens of  $>1$  rickettsial species.

**Case definitions.** A case of confirmed ATBF was defined as a flulike illness commencing no later than 10 days after the patient left rural areas in sub-Equatorial Africa and with positive suicide PCR and/or definite serological evidence of *R.*

*africae* infection. A case of probable ATBF was defined as a flulike illness commencing no later than 10 days after the patient left rural areas in sub-Equatorial Africa, with serological evidence of recent nondeterminable SFG rickettsial infection, and for which at least 1 of the patient's fellow travelers had similar symptoms and had confirmed ATBF diagnosed. A case of nonspecific SFG rickettsiosis was defined as a flulike illness commencing no later than 10 days after the patient left rural areas in sub-Equatorial Africa, with serological evidence of recent nondeterminable SFG rickettsial infection, and for which none of the patient's fellow travelers had confirmed ATBF diagnosed.

**Statistical analyses.** All data were analyzed using SPSS software, version 11.0 (SPSS). For comparison of variables, we used the  $\chi^2$  test, Fisher's exact test, and Student's *t* test of means, when appropriate. The crude magnitude of the association between possible risk factors and seropositivity was measured with ORs and 95% CIs. Variables included in the univariate logistic regression model were age, male sex, travel to southern Africa (South Africa, Swaziland, Lesotho, Namibia, and/or Botswana), travel during the summer (November–April), a stay in rural areas for >7 days, hunting as the purpose of travel, bush walk with limited personal protection against arthropod bites, and the use of primitive accommodations. Variables with a *P* value of <.10 were entered into a multivariate logistic-regression model. Observed differences were considered significant at *P* ≤ .05 for 2-tailed tests.

## RESULTS

A total of 1153 attendees were requested to participate in the study; of these, 1133 (98.3%) accepted. However, 57 attendees who had agreed to participate did not travel to rural areas, and 136 did not submit a completed questionnaire, leaving 940 travelers to rural sub-Equatorial Africa to be included in the study.

Among included travelers, there were 476 female (50.6%) and 464 male (49.4%) travelers, with a mean age of 37.0 years (median, 33 years; range, 4–86 years). There were 710 first-time travelers (75.5%) to rural sub-Saharan Africa. The main purposes of travel were leisure safari (44.7%), backpacking (23.1%), business (12.1%), visiting friends and relatives (11.0%), and game hunting (8.4%). There were 99 travelers (10.5%) who visited rural areas in >1 country. The 5 most common destinations were Kenya (26.5%), South Africa (25.8%), Tanzania (23.9%), Zimbabwe (7.1%), and Botswana (6.3%). Of the 420 people (44.7%) who travelled during the summer, April was the most popular month (15.2%). The mean length of stay in rural areas was 6.4 days (median, 5 days; range, 1–60 days), corresponding to a total time of 6016 person-days

(~200 person-travel-months); only 5 travelers (0.5%) stayed for >30 days in rural areas. Eighty-eight travelers (9.4%) used primitive accommodations in rural areas. Bush walk was reported by 511 travelers (54.4%), and, of these, 312 (61.1%) reported no or only limited use of personal protection against arthropod bites.

Of the 940 travelers, 143 (15.2%) reported flulike symptoms; of these, 83 presented for medical evaluation. Thirty-eight travelers (4.0% of the cohort and 26.6% of those reporting flulike symptoms) had ATBF diagnosed (27 with confirmed ATBF and 11 with probable ATBF). In addition, 12 travelers had nonspecific SFG rickettsiosis diagnosed, resulting in an overall incidence of SFG rickettsiosis of 5.3%, corresponding to 0.25 cases per person-travel-month.

Of the 38 patients with ATBF, 23 (61%) were first-time travelers to rural sub-Saharan Africa. The incidences of ATBF varied substantially among various groups of travelers: 20 (25.3%) of 79 for hunters, 3 (2.8%) of 107 for business travelers, 3 (2.6%) of 114 for visitors to friends and relatives, 9 (2.1%) of 420 for leisure travelers, and 3 (1.4%) of 218 in backpackers. In 15 (56%) of 27 confirmed ATBF cases, the infections occurred in clusters. Tick bites or ticks on clothes or skin were observed by 16 (48%) of 33 of patients with ATBF. After adjustment for the confounding effects of male sex, travel duration >7 days, the use of primitive accommodations, and bush walk with limited personal protection against arthropod bites, 3 factors were significantly associated with ATBF in a multiple logistic regression model: hunting as the purpose of travel, travel to southern Africa, and travel during the summer (table 1).

A selection of clinical characteristics of the patients with ATBF is presented in table 2. Most patients had myalgia, headache, and fever, whereas inoculation eschars and regional lymphadenitis were present in ~50% (figure 1). Multiple inoculation eschars (figure 2), ranging in number from 2 to 10, were observed in 21% of the patients. Of the patients who reported myalgia, virtually all complained about prominent neck muscle pain and stiffness. Fifteen patients (39%) were treated with antirickettsial treatment—13 were treated with doxycycline and 2 were treated with ciprofloxacin. Except for 1 patient who had a fever for another 5 days, all treated febrile patients defervesced within 48 h after the administration of antirickettsial therapy. Two (5%) of 38 patients were briefly hospitalized.

A complicated course was documented in 1 case: a 44-year-old HLA B27 antigen-negative woman developed a painful swelling in her right sternoclavicular joint 5 days after the onset of ATBF symptoms and 3 days after the administration of doxycycline treatment. No joint puncture was performed, but a diagnosis of reactive arthritis was made on clinical grounds. The patient's symptoms resolved with receipt of ciprofloxacin (500 mg b.i.d. for 3 weeks).

**Table 1. Findings of univariate and multivariate analyses of factors associated with African tick bite fever (ATBF) in 940 travelers to rural sub-Equatorial Africa.**

Variable	Patients with ATBF (n = 38)		Patients without ATBF (n = 902)		Univariate model		Multivariate model <sup>b</sup>	
	Value (%)	No. of travelers <sup>a</sup>	Value (%)	No. of travelers <sup>a</sup>	OR (95% CI)	P	OR (95% CI)	P
Mean age, years	38.3	38	36.9	889	—	.54	—	—
Male sex	26 (68)	38	438 (49)	902	2.30 (1.44–4.61)	.016	0.63 (0.25–1.62)	.34
Travel to southern Africa <sup>c</sup>	28 (74)	38	324 (36)	900	4.98 (2.39–10.38)	<.001	3.06 (1.27–7.41)	.013
Travel during summer <sup>d</sup>	27 (71)	38	388 (43)	901	3.25 (1.59–6.62)	.001	2.80 (1.22–6.44)	.015
Travel duration of >7 days	18 (50)	36	197 (23)	872	3.43 (1.75–6.71)	<.001	1.86 (0.82–4.20)	.13
Hunting as purpose of travel	20 (53)	38	59 (7)	900	15.84 (7.95–31.56)	<.001	10.18 (3.86–26.90)	<.001
Use of primitive accommodation	9 (24)	37	332 (38)	868	0.52 (0.24–1.11)	.087	0.83 (0.33–2.11)	.70
Bush walk with limited personal protection	19 (51)	37	301 (34)	877	2.02 (1.04–3.91)	.033	1.49 (0.69–3.24)	.31

<sup>a</sup> No. of travelers for whom this information was available.

<sup>b</sup> Done for variables with  $P < .10$  in the univariate model.

<sup>c</sup> South Africa, Swaziland, Lesotho, Namibia, and/or Botswana.

<sup>d</sup> November–April.

## DISCUSSION

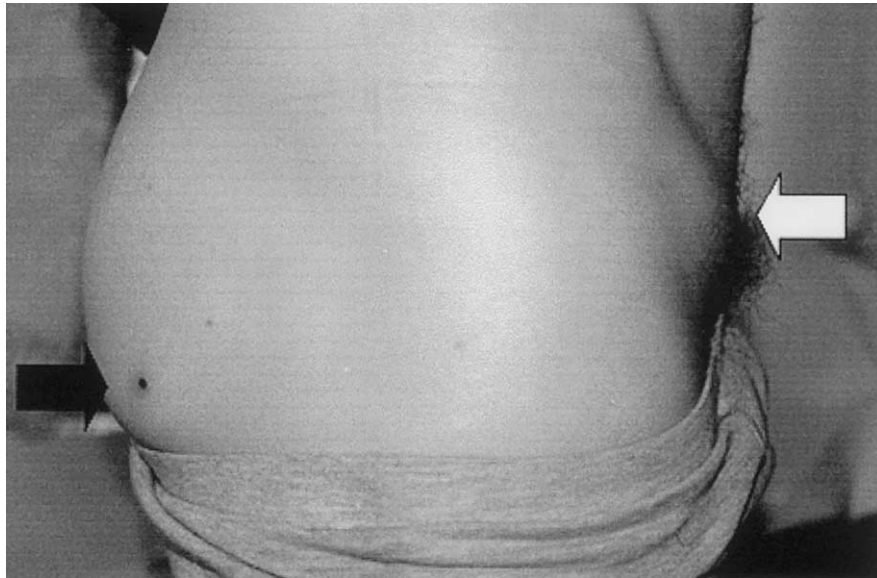
The story of travel-associated ATBF is an instructive one and highlights the medical consequences of modern mass tourism to the tropics. In fact, ATBF has now emerged from being a practically unknown entity outside areas of endemicity only a decade ago to be one of the more frequent causes of fever in today's travel medicine. The present study cohort, enrolled through travel-medicine clinics and consisting of mostly short-term and first-time safari tourists, is probably representative of many, if not most, of today's international travelers to rural sub-Saharan Africa. Our data could therefore be of potential interest to many health care providers, tour operators, and presumptive travelers.

**Table 2. Clinical characteristics of 38 consecutive patients with travel-associated African tick bite fever.**

Characteristic	n/N (%)
Fever <sup>a</sup>	29/36 (81)
Headache	30/36 (83)
Myalgia	33/38 (87)
Inoculation eschar	
Single	12/38 (32)
Multiple	8/38 (21)
Regional lymphadenitis	18/37 (49)
Cutaneous rash	
Musculopapular	10/38 (26)
Vesicular	6/38 (16)
Aphthous stomatitis	4/38 (11)

<sup>a</sup> Temperature >37.5°C.

**Epidemiology.** First, our estimated incidences of ATBF (4.0%–5.3%) are notable and widely exceed those reported for other tropical fevers in short-term travelers to tropical Africa, including malaria, relapsing fever, African trypanosomiasis, and typhoid fever [17, 18]. In fact, because only 58% of the travelers who reported flulike symptoms presented for medical evaluation, the true incidence of ATBF might have been even higher in the present cohort. Our estimates, which are consistent with those of a recent seroepidemiological study of Norwegian first-time travelers to rural sub-Equatorial Africa [19], could probably be largely explained by the unique features of the involved tick vectors: *Amblyommas* are widely present on the vegetation at many popular wildlife attractions in sub-Saharan Africa [8, 20–23], they are frequently (up to 70%) infected with *R. africae* [24–26], and they are notoriously aggressive and readily bite humans [27]. Second, those at highest risk for acquiring ATBF in the present study were game hunters—travelers known to be extensively exposed to ground vegetation and high grass, as well as to ungulates and their hides [12, 28]. However, it is important to recognize that other groups of travelers, such as leisure safari tourists and business travelers, may also be infected, some during even brief visits to rural areas. Third, although *R. africae* infection appears to be widespread in most parts of rural sub-Equatorial Africa, the risk of acquiring ATBF in the present study varied significantly between travelers to the 2 major safari destinations on the continent, southern and East Africa. The reason for this geographical difference, which is supported by most published case reports of travel-associated ATBF [1], is unknown, but it may involve factors such as various strains of *R. africae*, varying transmission efficacy of the 2 principal vectors (*A. hebraeum* in southern Africa and *A.*

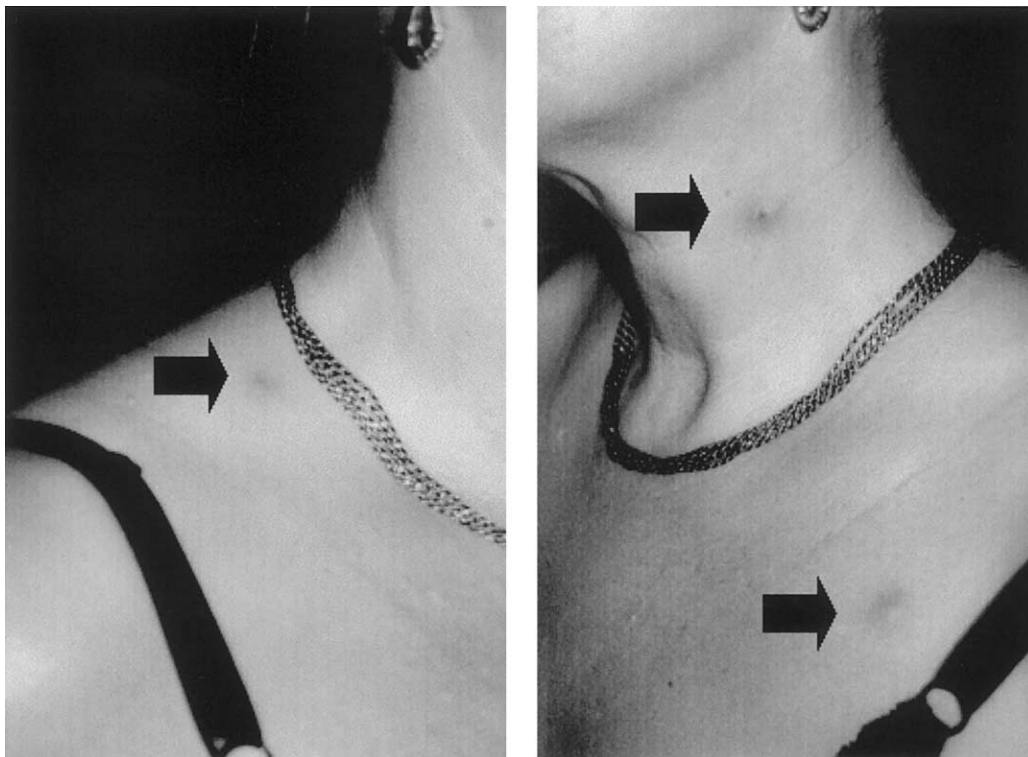


**Figure 1.** A 30-year-old man with a single inoculation eschar on his buttock (*black arrow*) and regional lymphadenitis in his groin (*white arrow*)

*variegatum* in East Africa), or, possibly, various risk behaviors among travelers. Fourth, although cases are encountered year-round, our data indicate that the risk of acquiring travel-associated ATBF is highest during the rainy summer, when tick abundances peak in most areas of endemicity [21]. Last, with 56% of the cases being clustered, our data underscore that

clusters are important epidemiological features of ATBF, as opposed to the other SFG rickettsioses endemic to sub-Saharan Africa [1, 9–14].

**Presentation.** In contrast to previously reported cases [1, 9–13, 28–34], the full-blown clinical picture of ATBF was rarely seen in our prospective series. Nonspecific flulike features dom-



**Figure 2.** A 50-year-old woman with multiple inoculation eschars on her thorax and neck (*arrows*)

inated the clinical presentations, and inoculation eschars, regional lymphadenitis, and vesicular rash, which are considered to be the clinical hallmarks of ATBF, were seen in only  $\leq 50\%$  of the cases. Notably, multiple inoculation eschars, a pathognomonic feature of ATBF that is related to the unique aggressive behavior of the involved tick vectors, were documented in only 21% of our cases, as opposed to 45% in a large retrospective series [1]. Of interest, prominent neck-muscle myalgia and nuchal stiffness, which have been reported elsewhere in patients with Rocky Mountain spotted fever caused by *Rickettsia rickettsii* [35], were common in our series and may reflect transient infection of the CNS. Aphthous stomatitis has never been documented in other SFG rickettsioses and seems to be a distinct, albeit rare, clinical sign of ATBF [9, 32]. The underlying pathophysiological process is unknown but may include rickettsial infection of the oral mucosa, immunological reactions, or both.

Only 41% of our patients were treated with antirickettsial agents, a finding that contrasts that of a large retrospective series in which 86% of patients with ATBF received such treatment [1]. The status of chemotherapy for ATBF, including the choice of agent, indications, and dosing, is uncertain and has never been evaluated in clinical trials. However, as suggested by the present data and several case reports [1, 9–13, 28–34], treatment with tetracyclines, and possibly also with fluoroquinolones, seems to be associated with the rapid clinical improvement in most patients.

**Prophylactic measures.** Many travelers to rural sub-Saharan Africa are not provided with any specific pretravel information on ATBF or other tickborne diseases [19]. Such information is obviously needed, at least in the high-risk setting. Effective protection against tick bites during a stay in rural sub-Saharan Africa, however, may be difficult to accomplish. First, the meticulous wearing of boots, pants, and long-sleeved shirts may be considered too warm and inconvenient in tropical climates and was only done by a minority of the bush walkers in our study. Second, tick larvae and nymphs, the 2 tick stages that are most prone to bite humans, are minute and difficult to spot [27]; typically,  $<50\%$  of our patients with ATBF reported to have observed ticks on themselves. Third, permethrin, a synthetic pyrethroid and an effective acaricide for the treatment of clothing [36], is not readily available in many countries because of national regulations [37]. Fourth, the repellent efficacy of most insect skin repellents against the vectors of ATBF is unknown but is likely to be short-lasting, as was demonstrated for 20% lotions of diethyl-toluamide and KBR 3023, a recently developed piperidine compound [38]. Fifth, no vaccines are available for any SFG rickettsioses. Finally, although it is a possible option for selected travelers at high risk, chemoprophylaxis with fluoroquinolones or tetracycline has never

been evaluated in clinical trials and cannot currently be recommended.

In conclusion, our data suggest that ATBF may be common in short-term travelers to rural sub-Saharan Africa and that it may cause a significant proportion of flulike illnesses in travelers to this region. Pretravel health care counsellors should inform presumptive travelers about this risk, and, although hard data are still lacking, hunters and other travelers at high risk should be encouraged to take personal protective measures against tick bites during bush walks in areas of endemic. Clinicians should be aware of the frequent nonspecific presentation of ATBF.

## STUDY GROUP MEMBERS

Other members of the Norwegian African Tick Bite Fever Study Group were Bjørg Bjotveit (Ski Medical Center, Ski), Arne Brantsæter, (Bærum Hospital, Bærum), Helge Kjølshus (Fet Medical Center, Fetsund), Bjørn Gillhagen (Volvat Medical Center, Oslo), Herman Munthe-Kaas (Tåsen Medical Center, Oslo), Mohammed Saeme (Christiania Travel Clinic, Oslo), and Tor-Einar Vaage (Red Cross Medical Center, Oslo), Norway.

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