YALE JOURNAL OF BIOLOGY AND MEDICINE 93 (2020), pp.49-54.

CASE REPORT

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM
CELEBRATING 90 YEARS 1928–2018

# Probable African Tick Bite Fever in the United States

Kami Lowery[a] and Theodore Rosen[b,*]

[a]MD Program, Baylor College of Medicine, Houston, TX; [b]Department of Dermatology, Baylor College of Medicine, Jamail Specialty Care Center, Houston, TX

African tick bite fever (ATBF) is a tick-borne rickettsial disease most often observed in North American and European tourists returning home from the southern portion of Africa. Ticks infected with *Rickettsia africae* transmit this parasitic bacterium to humans, who subsequently develop an influenza-like illness, one or more inoculation eschars, and in some cases, a cutaneous rash. Because ATBF often presents with non-specific symptoms that suggest other infectious diseases, establishing the diagnosis may be difficult. Confirmatory assays, including serology and nucleic acid amplification, may take weeks to return and cannot help with acute treatment decisions. We present a case of a previously healthy 60-year-old woman who developed an illness strongly suggestive of ATBF after a missionary trip to Zimbabwe and discuss the disease's diagnostic challenges. Our paper also reviews the epidemiology of this disease and the currently available diagnostic laboratory tests and recommended treatment options.

## INTRODUCTION

African tick bite fever (ATBF) is an emerging infectious disease commonly seen in travelers returning from sub-Saharan Africa and, less frequently, the West Indies [1]. Patients typically experience acute onset of a flu-like illness 5 to 7 days after a tick bite and one or more eschars at the site of inoculation [2]. Infected ticks from the *Ambylomma* genus, transmit the pathogenic intracellular bacterium *Rickettsia africae* to a new host [1]. While cattle are the principal domestic host, *Ambylomma* ticks also parasitize other livestock and wild ungulates [1,3]. These ticks readily feed on humans, which explains why ATBF outbreaks often occur in clusters and people may have multiple eschars [1].

The *Ambylomma* ticks thrive in shaded areas with tall grasses and most commonly attack people on their legs before attaching in the warm, moist environment of the groin, axilla, or popliteal fossae [2]. After the incubation period, usually no more than 10 days, patients develop non-specific symptoms such as fever, headache, fatigue, and myalgia [2,3]. A majority (53-100%) of patients develop an inoculation eschar, and 21-54% have multiple eschars. Regional lymphadenitis can be seen

*To whom all correspondence should be addressed: Theodore Rosen, Department of Dermatology, Baylor College of Medicine, Jamail Specialty Care Center, 1977 Butler Street, Suite E6.200, Houston, TX, 77030; Tel: 713-798-6131, Fax: 713-794-7863, Email: rosen@bcm.edu.

Abbreviations: ATBF, African tick bite fever; SFGR, Spotted fever group rickettsia; RDTs, Rapid diagnostic tests; ELISA, Enzyme-linked immunosorbent assay; IFA, Immunofluorescence assay; PCR, Polymerase chain reaction; LFA, Lateral flow assay.

Keywords: African tick bite fever, travel medicine, tropical medicine, eschar, *Rickettsia africae*, *Ambylomma hebraeum*, rickettsia, spotted fever group rickettsia, Zimbabwe, tick-borne rickettsial disease

Author Contributions: Dr Rosen was the treating physician. Both Dr. Rosen and Ms. Lowery participated in reviewing the data and writing/editing the manuscript.

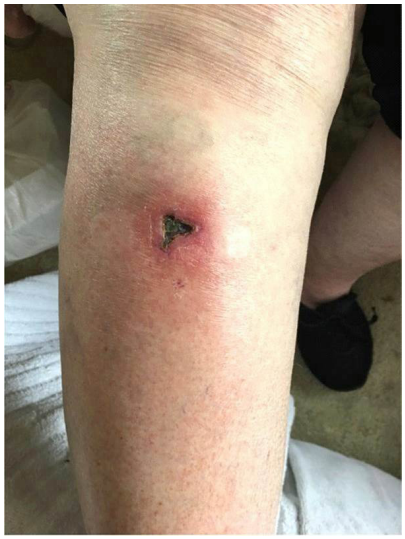

**Figure 1**. Eschar on lower leg at presentation.

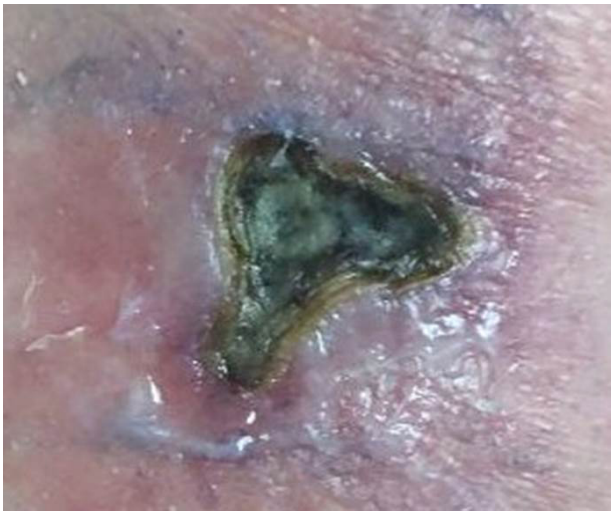

**Figure 2**. Close up view of eschar.

with or without an eschar. A generalized cutaneous rash, usually maculopapular or vesicular, appears in 15-46% of patients [2]. Aphthous stomatitis and lymphangitis are less common manifestations of this rickettsiosis [3]. Possible but extremely rare complications from ATBF include reactive arthritis, encephalitis, myocarditis, and neuropathy, but no fatalities have been reported [3]. The recommended treatment for adults and children with ATBF is doxycycline 100 mg twice daily for 5 to 7 days. Symptom relief and declining fever typically occurs within 48 hours of starting antibiotics [4].

Although endemic areas have spotted fever group rickettsia (SFGR) infection Seroprevalence rates of up to 70% [2], few reports of ATBF in indigenous people exist, likely due to under recognition of unapparent or mild disease [4]. The disease is frequently observed in safari tourists, game reserve visitors, and travelers participating in other outdoor activities such as camping and hiking. Walking in areas with infected ticks and brushing against vegetation places people at risk: ATBF is a zoonotic disease and is not spread from person to person [5]. Herein, we describe an isolated case study of likely and presumed ATBF in a middle-aged female traveler from the United States with no comorbidities.

## CASE PRESENTATION

This previously healthy 60-year-old white female presented in March with influenza-like symptoms and an eschar on her right leg shortly after completing a three-month mission trip in rural Zimbabwe. During her trip, she denied visiting any other African country, and the village she worked in was in northeast Zimbabwe, far from South Africa.

One week after the patient returned to the United States, she developed fever, headache, and diffuse myalgia. Shortly thereafter, she noticed a faint rash on her torso and a large, tender pustule on her right leg. The rash completely spared both palms and soles. She presented to her dermatologist 12 days after her return from Africa because the pustule evolved into an eschar. She did not recall a tick bite or anyone else with similar symptoms in Zimbabwe. Notably, she stayed in a rural village with tall grasses and many cattle in the area. She had no other medical problems and did not take any medications.

When she was evaluated in office, her temperature was 103°F, blood pressure was 178/98 mmHg, and heart rate was 115 beats per minute. Physical examination revealed a non-specific, scant maculopapular eruption on her trunk, a crusting black eschar with surrounding erythema on her proximal right shin, and tender inguinal adenopathy ipsilateral to the eschar (Figures 1 and 2). The patient was sent to the hospital for admission due to concerns about the eschar, rash, fever, and elevated blood pressure. Laboratory studies showed a decreased white blood cell count of 2,400 cells/mm$^3$, but her other labs were within normal limits. The primary team consulted dermatology.

After evaluating the patient, we immediately suspected an infection. We considered a wide range of infectious diseases, including bacterial sepsis, invasive fungal infection, tularemia, scrub typhus, plague, anthrax, and ecthyma gangrenosum [6]. Due to travel to and temporary residence in southern Africa, South African tick bite and African tick bite fever were also considered. Several etiologies were ruled out because the patient had an unremarkable medical history. Mucormycosis typically infects the nares of diabetic patients [7]; invasive fungal disease

**Table 1. Eschar-forming febrile diseases seen in travelers.**

| Disease | Symptoms | | | | |
|---|---|---|---|---|---|
| | Fever | Eschar | Rash | Headache | Myalgia |
| Anthrax | ✔ | ✔ | | ✔ | |
| Tularemia | ✔ | ✔ | ✔ | ✔ | |
| Scrub Typhus | ✔ | ✔ | ✔ | ✔ | ✔ |
| Plague | ✔ | ✔ | ✔ | ✔ | ✔ |
| Rickettsia | ✔ | ✔ | ✔ | ✔ | ✔ |

**Table 2. Tests done for eschar-forming exotic diseases.**

| Disease | Serology | Culture | Molecular Testing | Result |
|---|---|---|---|---|
| Anthrax | ELISA [a] antibody titers against protective antigen (PA) | *Bacillus anthracis* isolation? | Not performed | Both negative |
| Tularemia | ELISA [a] antibody titers | *Francisella tularensis* isolation? | Not performed | Both negative |
| Scrub Typhus | IFA [b] antibody titers | Not routinely done | PCR [c] | IFA negative |
| Plague | LFA antibody detection of F1 capsular antigen | *Yersinia pestis* isolated? | Not performed | Both negative |
| African Tick Bite Fever | ELISA [a] antibody detection | Not routinely done | PCR [c] | ELISA and PCR positive |

[a] Enzyme-linked immunosorbent assay, [b] Immunofluorescence assay, [c] Polymerase chain reaction, [d] Lateral flow assay.

is seen in chronically ill patients with comorbidities such as neutropenia, malignancy, or immunosuppression [8].

Given the patient's travel history and good baseline health status, we narrowed the differential diagnosis to exotic diseases such as anthrax, tularemia, scrub typhus, plague, and rickettsiosis. We compared her signs and symptoms with the typical features of these rare eschar-forming infections (Table 1). With the evidence strongly favoring African Tick Bite Fever, we performed a detailed work-up, including a tissue biopsy. We started the patient on empiric treatment with oral doxycycline 100 mg twice daily and she became afebrile within 2 days. Wound care for the eschar included wet-to-dry dressings and antibiotic ointment.

One week after the biopsy, the pan-*rickettsia* tissue PCR assay came back positive. One more week passed before indirect enzyme immunoassay for the detection of IgG class antibody directed against the "Spotted Fever Group" rickettsia showed a positive titer. Gene amplification and sequencing was not done. Tests for other potential diagnoses were negative (Table 2). The eschar gradually healed, but left a dyschromic and depressed scar on her leg (Figures 3 and 4). The patient otherwise fully recovered from her illness.

## DISCUSSION

*Rickettsia* is a genus of obligate intracellular bacteria with a worldwide distribution. These vector-borne microbes have a diverse host range and, in humans, can cause febrile illnesses ranging from mild to life threatening [9]. Fortunately, the antibiotic doxycycline can effectively treat human rickettsial infections [10].

Within the genus, the tick-borne spotted fever group rickettsioses (SFGR) includes *R. africae*, the pathogen responsible for African Tick Bite Fever*; R. conorii,* the pathogen responsible for South African tick bite fever; *R. rickettsii,* the causative agent of Rocky Mountain Spotted Fever in North America, among many others [11]. Although these bacteria cause illnesses that vary widely in severity, affected patients typically present with similar signs and symptoms, namely: fever, headache, and rash [10].

Multiple laboratory methods can confirm tick-borne rickettsial diseases. However, rapid diagnostic tests (RDTs) are usually not available, even in the United States [11]. Providers must use clinical and epidemiologic clues to make a presumptive diagnosis and start empiric antibiotic treatment while awaiting confirmatory test results. In a tropical setting, these tests are rarely available at all. Diagnosing a rickettsiosis can be difficult when the

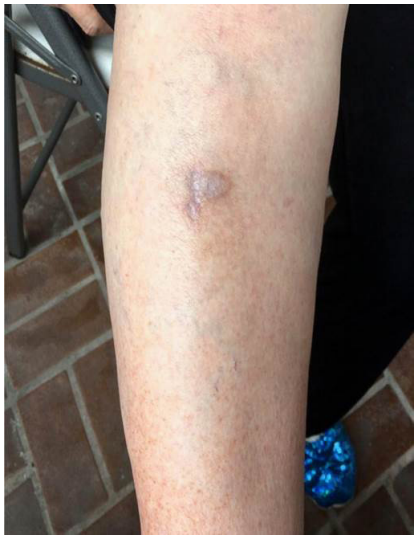

**Figure 3**. Healed skin lesion, depressed and hypochromic scar.

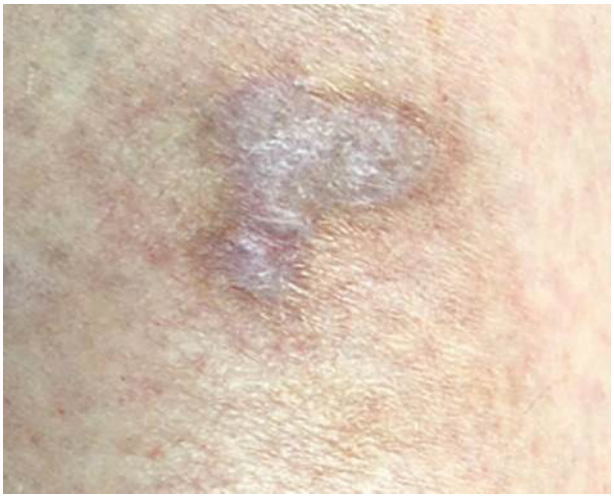

**Figure 4**. Close up view of final scar.

patient's presentation mimics other tropical diseases endemic to the area, or the typical clinical signs are absent [12]. For example, the classic clinical triad of rash, fever, and eschar only occurs in 50-75% of ATBF cases [4].

Luckily, our patient presented with all three clinical signs. The eschar helped us rule out non-eschar forming febrile illnesses such as malaria, dengue fever, and typhoid fever [6,13,14]. This finding was also critical because in the absence of an eschar, the non-specific ATBF rash can suggest a wide range of diseases: typhoid, measles, rubella, disseminated gonococcal disease, secondary syphilis, leptospirosis, arboviral and enteroviral infections, drug reactions, or vasculitis. Conversely, in the absence of the rash, the ATBF eschar can also resemble an early cutaneous anthrax lesion, an infected insect bite, or other skin trauma [4]. Given this wide differential, the importance of confirmatory testing for rickettsial etiology is clear.

Despite the presence of compatible clinical signs and symptoms, we were not able to completely rule out the diagnosis of South African tick bite fever (SA-TBF). Serologic and tissue testing was merely confirmatory of a rickettsial etiology, and SA-TBF is acquired in a similar geographic area and presents very similarly [15]. However, in our clinical estimation, this patient most likely had ATBF, because she was almost exclusively in a rural setting (where SA-TBF is almost always acquired in an urban setting). Moreover, while she was exposed to cattle and other livestock, she had virtually no exposure to dogs or kennels, the places where *R. conorii* is typically acquired [15]. Her rash completely spared the palms and soles, areas often affected by the eruption associated with SA-TBF; and her illness was quite mild, which contrasts with the more severe multi-system illness often associated with SA-TBF [15].

The currently available tests for rickettsial disease fall into three categories: nucleic acid amplification, culture, and serology. The serologic tests include enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assays (IFAs), and rapid diagnostic tests (RDTs) [13]. Notably, culture is rarely performed [11]. In this particular case, positive pan-*Rickettsia* tissue PCR and positive IgG serology clearly suggests a rickettsial etiology. However, without gene amplification and sequencing, one cannot be definitive as to the etiologic species. As elaborated previously, epidemiologic factors, including the temporal sequence of events, as well as observed clinical features strongly suggest the specific diagnosis of AFTB, but do not prove it. In fact, since all rickettsial species in the "Spotted Fever Group" share the same lipopolysaccharide antigens, a weakness of both ELISA and IFA assays is that cross-reactivity precludes species level identification.

We are aware that the rickettsioses are a group of emerging and reemerging diseases due to recent advances in molecular diagnostics and increased clinical awareness [9]. Although nucleic acid amplification tests (NAAT) are promising, such assays still require considerable improvement. Limited data suggest that the sensitivity of a pan-*Rickettsia* assay on an eschar sample or skin biopsy is only 43% [13]. Given the test's low sensitivity, we were fortunate that this assay helped suggest the most likely diagnosis. Although the test only identified the *Rickettsia* genus, more specific PCR assays can target unique gene regions to identify species and subspecies [13]. These tests were not readily available to us, but would not have really changed our management.

Specimens for molecular testing can be collected via an eschar biopsy, scab from the eschar surface, or a

swab of eschar exudate [11]. We performed a biopsy on live tissue underneath the eschar in order to maximize our PCR assay's sensitivity. Had we been in a field setting, we might have chosen one of the other, less invasive, options. The literature supports this approach: one prospective study confirmed ATBF in three patients with negative serology by using PCR on eschar swabs and/or crusts [14]. Other studies have reported similar findings about the utility of eschar swabs and crusts in diagnosing both ATBF and SA-TBF [15-17]. However, collecting an eschar swab involves lifting the scab partially or completely and vigorously swabbing the ulcerated area [18]. We chose to perform a biopsy because the necessary equipment was readily available, and the patient would have needed local anesthesia for either procedure.

In addition to demonstrating the diagnostic challenges related to rickettsial illness, this case also presents several travel medicine learning points. Although our patient visited her dermatologist for evaluation, a similar patient might see a primary care physician, an urgent care clinic, or an emergency department. Providers who work in any of these settings need to be cognizant of the wide range of common febrile diseases in travelers returning from sub-Saharan Africa. While our patient lived in Zimbabwe for three months, even short-term visitors to the region are also at risk [19]. This point is best illustrated by a prospective cohort study that identified key epidemiologic and clinical aspects of ATBF. In a group of 940 Norwegians who traveled to rural sub-Saharan Africa, the mean length of stay was 6.4 days. Only five (0.5%) travelers stayed for more than 30 days. Researchers estimated an incidence of ATBF of 4.0-5.3% in this cohort, which far surpasses the reported incidence of other tropical diseases in short-term travelers to the region, including typhoid fever, malaria, relapsing fever, and trypanosomiasis [19]. The high incidence of ATBF in short-term travelers suggests that our patient had a very high risk of contracting the disease given her significantly longer exposure time. The same study found three independent risk factors for ATBF in a multivariate logistic-regression model: travel to Southern Africa, travel during November through April, and game hunting [19]. Our patient fulfilled two of these three risk factors because she stayed in Zimbabwe from January to March. *Amblyomma hebraeum*, an important reservoir and the primary tick vector for *R. africae* in southern Africa [2,20], has high adult numbers during the rainy summer season in Zimbabwe with a peak from February to May [21]. Thus, our patient was in Zimbabwe at the most hazardous time of the year for ATBF. Also, she was exposed to the *Amblyomma* ticks' preferred habitat, tall grasses, and their most important host, cattle. In endemic areas, infection rates of *A. hebraeum* ticks with *R. africae* bacteria can exceed 70% [2].

In the context of this case, education about potential diseases seen in or near her intended destination, prior to travel, might have helped mitigate her risk. For example, she might have planned her trip at a different time of year. When counseling patients who are planning travel to sub-Saharan Africa, clinicians should discuss risk factors for ATBF, SA-TBF, and other potential infectious diseases, such as those noted in our initial differential diagnosis [22]. Providers could also develop and distribute a one-page information sheet to prospective travelers.

## CONCLUSIONS

We can take away several key points from this case. When evaluating a patient with a febrile illness of unknown or uncertain etiology, clinicians must obtain a detailed travel history, ask about exposure to vectors such as arthropods and other animals, and consider diseases common to the region the patient visited. Clinical and epidemiologic clues are critical for making such challenging diagnoses and support starting appropriate anti-infective therapy based upon a presumed diagnosis.

## REFERENCES

1. Althaus F, Greub G, Raoult D, Genton B. African tick-bite fever: a new entity in the differential diagnosis of multiple eschars in travelers. Description of five cases imported from South Africa to Switzerland. Int J Infect Dis. 2010 Sep 1;14:e274–276.
2. Jensenius M, Fournier P-E, Kelly P, Myrvang B, Raoult D. African tick bite fever. Lancet Infect Dis. 2003 Sep 1;3(9):557–564.
3. Roch N, Epaulard O, Pelloux I, Pavese P, Brion J-P, Raoult D, Maurin M. Ambylomma hebraeum. Clin Infect Dis. 2008 Aug 1;47(3):e28–35.
4. Frean J, Blumberg L, Ogunbanjo G. Tick bite fever in South Africa. South African Family Practice. 2014 Aug 15;50:33–35.
5. IAMAT. African Tick-Bite Fever [Internet]. [cited 2019 Jul 9]. Available from: https://www.iamat.org/risks/african-tick-bite-fever
6. Dunn C, Rosen T. The rash that leads to eschar formation. Clin Dermatol. 2019 Mar 1;37(2):99–108.
7. Kauffman CA, Malani AN. Zygomycosis: an emerging fungal infection with new options for management. Curr Infect Dis Rep. 2007 Nov;9(6):435–440.
8. Acosta J, Catalan M, Palacio-Pérez-Medel A, Montejo J-C, De-La-Cruz-Bértolo J, Moragues M-D, Pontón J, Finkelman MA, Palacio A. Prospective study in critically ill non-neutropenic patients: diagnostic potential of (1,3)-β-D-glucan assay and circulating galactomannan for the diagnosis of invasive fungal disease. Eur J Clin Microbiol Infect Dis. 2012 May;31(5):721–731.
9. Merhej V, Angelakis E, Socolovschi C, Raoult D. Genotyping, evolution and epidemiological findings of Rickettsia species. Infect Genet Evol. 2014 Jul 1;25:122–137.
10. Drexler NA, Dahlgren FS, Heitman KN, Massung RF, Paddock CD, Behravesh CB. National Surveillance of

Spotted Fever Group Rickettsioses in the United States, 2008–2012. Am J Trop Med Hyg. 2016 Jan 6;94(1):26–34.
11. Biggs HM. Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis — United States. MMWR Recomm Rep [Internet]. 2016 [cited 2019 Jul 10];65. Available from: https://www.cdc.gov/mmwr/volumes/65/rr/rr6502a1.htm
12. Parola P, Raoult D. Tropical rickettsioses. Clin Dermatol. 2006 May 1;24(3):191–200.
13. Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. Curr Opin Infect Dis. 2016 Oct;29(5):433–9.
14. Socolovschi C, Renvoisé A, Brouqui P, Parola P, Raoult D. The use of eschar swabs for the diagnosis of African tick-bite fever. Ticks Tick Borne Dis. 2012 Dec 1;3(5):361–3.
15. Frean J, Grayson W. South African Tick Bite Fever: An Overview. Dermatopathology (Basel). 2019 Jun 26;6(2):70–76.
16. Nilsson K, Wallménius K, Rundlöf-Nygren P, Strömdahl S, Påhlson C. African tick bite fever in returning Swedish travellers. Report of two cases and aspects of diagnostics. Infect Ecol Epidemio. 2017 Aug 2;7:1343081.
17. Harrison N, Burgmann H, Forstner C, Ramharter M, Széll M, Schötta A, Stanek G, Markowicz M. Molecular diagnosis of African tick bite fever using eschar swabs in a traveller returning from Tanzania. Wien Klin Wochenschr. 2016 Aug 3;128.
18. Information for Health Care Providers. Other Spotted Fevers . CDC [Internet]. [cited 2019 Jul 25]. Available from: https://www.cdc.gov/otherspottedfever/healthcare-providers/index.html
19. Jensenius M, Fournier P-E, Vene S, Hoel T, Hasle G, Henriksen AZ, Hellum KB, Raoult D, Myrvang B, Norwegian African Tick Bite Fever Study Group. African Tick Bite Fever in Travelers to Rural Sub-Equatorial Africa. Clin Infect Dis. 2003 Jun 1;36(11):1411–1417.
20. Kelly PJ, Beati L, Mason PR, Matthewman LA, Roux V, Raoult D. Rickettsia africae sp. nov., the etiological agent of African tick bite fever, Int J Syst Bacteriol, 1996 Apr;46(2):611-614.
21. Petney TN, Horak IG, Rechav Y. The ecology of the African vectors of heartwater, with particular reference to Amblyomma hebraeum and Amblyomma variegatum. Onderstepoort J Vet Res. 1987;54(3):381–95.
22. Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, Keystone JS, Pandey P, Cetron MS. Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers. N Engl J Med. 2006 Jan 12;354(2):119–30.