Tick bite fever and Q fever – a South African perspective

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Tick bite fever (TBF) and Q fever are zoonotic infections, highly prevalent in southern Africa, which are caused by different genera of obligate intracellular bacteria. While TBF was first described nearly 100 years ago, it has only recently been discovered that there are several rickettsial species transmitted in southern Africa, the most common of which is *Rickettsia africae*. This helps to explain the highly variable clinical presentation of TBF, ranging from mild to severe or even fatal, that has always been recognised. Q fever, caused by *Coxiella burnetii*, is a protean disease that is probably extensively under-diagnosed. Clinically, it also shows a wide spectrum of severity, with about 60% of cases being clinically inapparent. Unlike TBF, Q fever may cause chronic infection, and a post-Q fever chronic fatigue syndrome has been described. The molecular pathophysiology of these diseases provides insight into different strategies that intracellular parasites may use to survive and cause disease. While newer macrolide and quinolone antibiotics show activity against these pathogens and may be useful in young children and pregnant women, the treatment of choice for acute infection in both diseases is still tetracycline-group antibiotics. Chronic Q fever remains challenging to treat.

The genera *Rickettsia* and *Coxiella* are aerobic Gram-negative obligate intracellular bacteria that utilise a variety of invertebrate and vertebrate hosts as vectors and reservoirs of infection. Humans are generally accidental hosts and are not required to maintain natural transmission cycles. Louse-borne typhus is no longer the major public health problem it once was in South Africa,[1] and in southern Africa rickettsiae are now best known as agents of tick bite fever (TBF); although *Coxiella burnetii*, the cause of Q fever, is also widespread in the region, it is far less often identified as a cause of human disease. These two conditions are the focus of this brief review.

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Taxonomy and classification

Molecular taxonomic methods based on ribosomal and other gene nucleotide sequence homologies have allowed more than 30 species and subspecies of rickettsiae to be distinguished to date.[2] Before the availability of these modern techniques, rickettsiae were divided on clinical and serological criteria into three groups: the spotted fever group, the typhus group, and scrub typhus. The sole agent of scrub typhus has been assigned to a new genus and is now called *Orientia tsutsugamushi*. Historically, several diseases in the first two groups have been recognised in southern Africa; while scrub typhus could potentially be seen in returning travellers, it does not occur naturally in the region. Molecular taxonomy now places the agent of Q fever, *C. burnetii*, in the γ-proteobacteria, order *Legionellaceae*, whereas the rickettsiae are classified as α-proteobacteria, order *Rickettsiales*, family *Rickettsiaceae*.[2] Subdivision of the genus *Rickettsia* into spotted fever and typhus groups has phylogenetic validity as well as clinical and epidemiological relevance.

Prevalence of the diseases

Boutonneuse fever (also called Mediterranean spotted fever) was first described in Tunis in 1910 as a disease associated with sandfly bites.[3] Although he did not initially make the connection with tick bites and ascribed the condition to a variant of paratyphoid fever, McNaught, a British Army doctor working in South Africa, had noted in 1908 the typical clinical findings of a febrile disease with a profuse rash,[4] and later entertained the suggestion of a colleague that similar cases followed tick bites.[5] In 1911, Sant'Anna[6] and Nuttall[7] independently recorded a disease in southern Africa closely resembling boutonneuse fever, associated with tick bites. In 1931 Troup and Pijper published their classic description of TBF, in which they explicitly stated that there were two distinct clinical forms of the disease, one mild and one more severe.[8] Pijper's observations and animal experiments, suggesting that different agents caused boutonneuse fever and TBF,[9] were superseded by others' work, and clinical variation in disease was ascribed to factors such as age-related differences in susceptibility and vector exposure. The result was that *Rickettsia conorii* var. *pijperi* became accepted as the only agent of South African TBF, although variation in epidemiology and clinical presentation was always acknowledged.[1,10] In 1992, however, Kelly *et al*. identified, by molecular techniques, a different rickettsial species responsible for some cases of TBF; this was subsequently named *Rickettsia africae*.[11] There are therefore at least two TBF diseases present in southern

Africa: boutonneuse fever-like TBF (caused by *R. conorii*) and African TBF (caused by *R. africae*). The latter is diagnosed far more commonly than the former in tourists,[12] but this group has a different risk profile compared with the typical resident population. *R. conorii* is usually transmitted by dog ticks in a peri-urban or peri-domestic setting, with dogs, rodents and ticks themselves forming the reservoir. In contrast, African TBF is typically transmitted by particular cattle and game ticks (*Amblyomma hebraeum* in southern Africa) in a rural setting. Clinical distinction between the two will be discussed later. From a disease burden aspect, surveys in sub-Saharan Africa have shown up to 70% seroprevalence in areas where *Amblyomma* ticks and cattle farming coincide.[13] Despite this there are very few clinical case reports of TBF in indigenous populations,[14] pointing to likely difficulties with clinical recognition and mild or inapparent disease in young people. When specifically sought, however, high rates of infection may be apparent in African countries: of 234 patients with acute febrile illness in southwest Cameroon, 32% had IgM antibodies to *R. africae*.[15] Annual case incidence rates of African TBF have been estimated as 60 - 80 per 10 000 patients in Zimbabwe recently.[16] In South Africa, TBF is commonly recognised in non-African patients but the incidence is not known. The incidence rate of infection has been estimated to be in the region of 4 - 5% in visitors from Europe, which is higher than those for other febrile illnesses such as malaria and typhoid fever. A large number of people are at risk, e.g. game reserve visitors, hunters, soldiers, and farmers.[17] It is likely that there are at least two other members of the spotted fever group of rickettsiae prevalent in southern Africa; Pretorius and Birtles recently reported a case each of TBF caused by *R. aeschlimannii* and *R. mongolotimonae*.[18,19] *R. africae* infections have emerged in the West Indies, where the usual vector outside of southern Africa, *A. variegatum*, was imported into Guadeloupe with cattle from Senegal in the 19th century, but has become widespread in the Caribbean region in the last 30 years.[20]

Q fever was first clinically characterised in 1935 during an outbreak of febrile illness in abattoir workers in Brisbane.[21] The agent, thought then to be a type of rickettsia, was subsequently isolated in Australia and the USA, and named *Coxiella burnetii* in 1948. Distribution is worldwide, except for Antarctica and New Zealand.[22] Like spotted fever group rickettsial diseases, Q fever is a tick-associated zoonosis, with an extremely wide host range. The traditional reservoirs of human importance are domestic stock: cattle, sheep, and goats; parturient domestic cats and dogs have also been sources of outbreaks.[22] Organisms localise to placenta and mammary glands, and while infections in animals are usually silent, they can cause outbreaks of abortion. *C. burnetii* differs in many ways from rickettsiae in being highly environmentally resistant, because of a spore-like stage; it shows antigenic phase variation; it produces a granulomatous rather than vasculitic pathology; and it demonstrates a potential for chronic infection. Most importantly, acquisition by humans is predominantly by the airborne route, especially when handling animal products of conception. Transmission via unpasteurised milk or by crushing ticks has rarely been described; tick bites are thought to be unimportant for human infections. Q fever was described as the most prevalent rickettsial infection in South Africa,[23] although its agent has since been assigned to a different taxonomic group. The seroprevalence in humans in South Africa is not known, although it is likely to be lower than in the past because of rapid urbanisation. In Zimbabwe a prevalence of antibodies to *C. burnetii* of 37% was recorded in humans in 1993.[24] Regarding animal seroprevalence, in South African cats and cattle rates were 2% and 8%, respectively; for Zimbabwe the corresponding figures were 13% and 39%, and 10% and 15% in goats and dogs, respectively.[24,25]

Pathophysiology

TBF rickettsiae, like those of other spotted fever agents, proliferate in microvascular endothelial cells and produce a multifocal, multi-organ vasculitis involving skin, brain, lungs, heart, liver, kidneys, adrenals, and other organs. At a molecular level, entry of spotted fever group rickettsiae is initiated by binding of outer membrane proteins OmpA and OmpB to a host cell receptor; for *R. conorii*, this is probably Ku70, a multifunctional protein of eukaryotic cells. The rickettsiae gain access to the cell interior by inducing changes in the actin cytoskeleton, leading to their being engulfed.[26] Once inside, they escape within minutes from the phagosome into the cytosol, and avoid destruction by lysosomal attack. The rickettsiae polymerise actin at one of their poles, resulting in movement through the cytoplasm and penetration of neighbouring endothelial cells, thereby affecting segments of vasculature. Rickettsiae do not produce exotoxins, and an important virulence mechanism is inducing oxidative stress on host cells. The end result of rickettsial proliferation, metabolic activity, and host immune response, is increased microvascular permeability and oedema, which leads to tissue and organ dysfunction; however, because lesions are localised, albeit multifocal, whole organ failure is generally uncommon.[26,27] Histologically, there is endothelial cell damage, necrosis, leakage, and platelet-fibrin thrombi, with endothelial proliferation and a perivascular mononuclear inflammatory cell infiltrate.

In contrast to the vasculitis caused by rickettsiae, the hallmark of *C. burnetii* infection is granulomatous inflammation. The organism targets macrophages and monocytes, and the two antigenic states of the organism are intimately linked to cell entry, intracellular survival, and ultimate elimination or persistence. The Toll-like receptor 4 (TLR4) plays a central role in pathogen uptake, cytokine response, and granuloma formation. Once internalised,

C. burnetii survives and replicates in acid vacuoles (pH 4.5); this contrasts with the cytoplasmic location of rickettsiae. Phase I forms are less efficiently phagocytosed; phase II mutants therefore proliferate more rapidly initially, and the antibody response is primarily directed at phase II organisms in acute infections. Although macrophages can kill phase II bacteria, phase I stages initially avoid death by inhibiting the final phagosome maturation step, but this function can be restored by γ-interferon. Ultimately, only phase I organisms may survive and persist. In chronic Q fever the immune response is ineffective, despite high levels of antibodies to both phases, and may cause harmful effects like leucocytoclastic vasculitis and glomerulonephritis.[28] Histologically, characteristic non-caseating 'fibrin ring' or 'doughnut' granulomas are found mainly in the liver, bone marrow and lungs. Other pathological changes include small vessel vasculitis and fatty change in the liver in some cases, and an interstitial pneumonitis with a mononuclear inflammatory cell infiltrate in the alveolar septa, plus fibrinous exudates in the alveolar air spaces.[29]

Clinical features

As indicated above, TBF is commonly diagnosed in South Africa, although recognised cases are probably far outnumbered by subclinical ones. Larval and nymph stage ticks typically transmit the diseases; feeding larvae, in particular, may not be noticed because they are so small. The typical clinical picture of *R. conorii* infections (boutonneuse fever-type TBF) begins, after an incubation period of 5 to around 7 days, with a consistent prodrome, comprising malaise, fever, headache, nightmares, and myalgia. The primary lesion, the eschar, marks the site of attachment of the infected tick, and consists of a central necrotic area surrounded by inflamed skin (Fig. 1). The eschar is not always found; it may be hidden under scalp hair, between the toes, or in the anogenital area. After about 3 days the rash appears; typically, it is a generalised coarse maculopapular eruption, the distribution of which includes the palms and soles (Figs 2 and 3). There is a spectrum of clinical presentation from very mild to severe and even fatal disease, the latter particularly in elderly or debilitated people, but not confined to this group. Complications include encephalitis, confusion, or coma, pneumonia, pulmonary embolism following deep-vein thrombosis, bleeding, gangrene, hepatorenal failure and myocarditis (Fig. 4). Rarely, but particularly when treatment is delayed, TBF can manifest with multi-organ involvement, and resemble septicaemia or even a viral haemorrhagic fever such as Crimean-Congo haemorrhagic fever (CCHF). In the latter the tick responsible for virus transmission is a *Hyalomma* species, and the characteristic eschar at the bite site is absent. The incubation period from tick bite to clinical disease differs in the two diseases; 1 - 3 days following tick-transmitted CCHF, and usually at least 7 days in TBF. African TBF (*R. africae*) tends to be a milder disease in general, and life-threatening

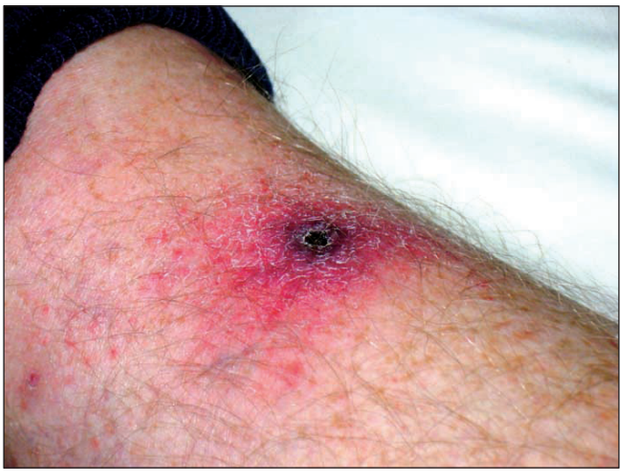

Fig. 1. Tick bite fever eschar (photo: author's collection).

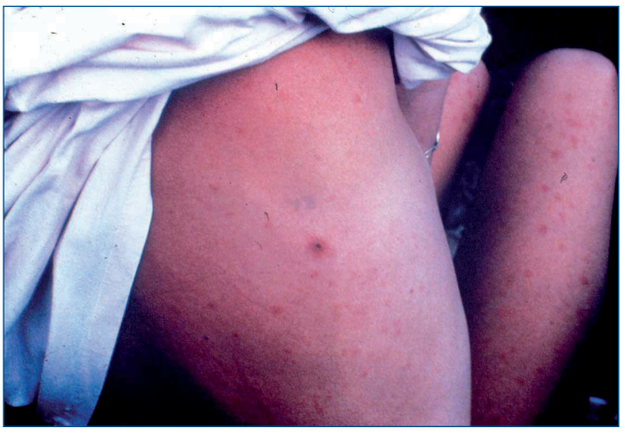

Fig. 2. Typical coarse maculopapular rash of tick bite fever (photo: B Miller).

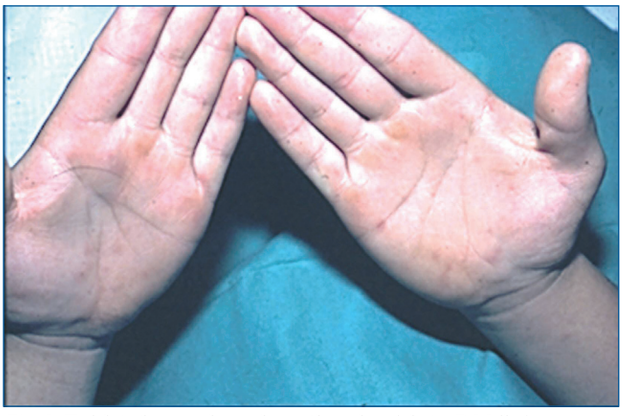

Fig. 3. Tick bite fever rash involving the palms (photo: B Miller).

complications have not been described.[13,17] The prodrome is similar to that of *R. conorii* infection; characteristic, but not consistent, distinguishing features are multiple eschars, tender regional lymphadenopathy, rashless illness, or only scattered

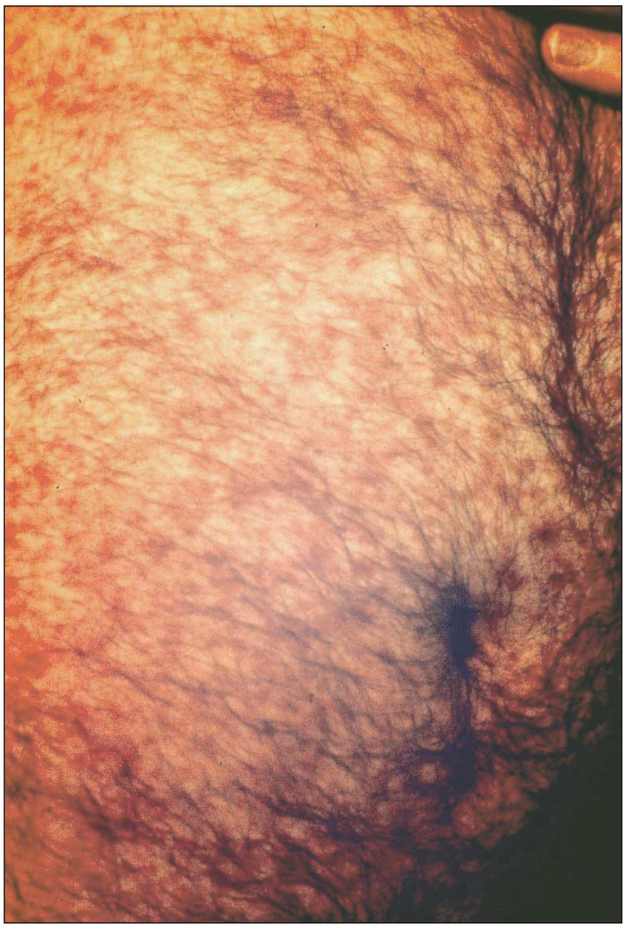

Fig. 4. Confluent rash in severe, complicated tick bite fever (photo: B Miller).

and/or vesicular rash elements. Aphthous stomatitis was noted in 11% of a series of 38 patients.[17] Unusual clinical features of African TBF have included transient neuropsychiatric symptoms including depressed mood,[30] acute myocarditis,[31] and subacute neuropathy.[32]

Up to 60% of *C. burnetii* infections are asymptomatic; typical acute presentations include a self-limited febrile illness, pneumonia, hepatitis, neurological involvement (encephalitis, meningoencephalitis, Guillain-Barré syndrome, other neuropathies), and fetal loss in pregnancy.[28] Q fever is an important cause of community-acquired 'atypical' pneumonia. The clinical presentation is variable; cough is often absent; the illness is usually mild to moderately severe, but sometimes progresses rapidly to an acute respiratory distress syndrome and respiratory failure. Clinically and radiologically, Q fever pneumonia is indistinguishable from other atypical pneumonias; multiple rounded opacities on chest radiographs have been described, but this is not a consistent feature.[22] Q fever hepatitis presents in three ways: a predominantly infectious hepatitis picture; an incidental finding during acute Q fever; and a fever of unknown origin picture, proven by typical histology of liver biopsy. A study in France estimated that the rate of clinical Q fever was 13 times higher in HIV-positive patients than in the general population.[33] Skin involvement may take the form of punctiform or maculopapular rashes or erythema nodosum.[28] The recognised acute clinical spectrum has expanded to include acalculous cholecystitis, rhabdomyolysis, endo-, myo- and pericarditis, glomerulonephritis and haemolytic uraemic syndrome, among others.[34] Inapparent Q fever may be acquired concomitantly or consecutively with other tickborne infections.[35] Chronic Q fever classically manifests as endocarditis, typically infecting previously damaged valves; rarely, aneurysms or vascular grafts may be infected; osteomyelitis, hepatitis, prolonged fever, and persistent infection in pregnancy are other uncommon chronic presentations. An emerging third category of infection is long-term sequelae after acute disease, particularly chronic fatigue syndrome.[34]

Diagnostic issues

The classic clinical triad of fever, eschar and rash occurs in 50 - 75% of cases of TBF; a number of other conditions may need to be considered in less typical presentations. The eschar may resemble an infected insect bite or other skin trauma, or an early anthrax lesion. Depending on severity, the rash may suggest rubella, measles, secondary syphilis, disseminated gonococcal disease, enterovirus or arbovirus infections, leptospirosis, typhoid, immune complex vasculitis, or drug reactions. Meningococcal rashes can look similar, but the illness is much more acute than TBF. During the prodromal period before the appearance of the rash, malaria is an important differential diagnosis in travellers. Laboratory diagnosis is usually made by serological tests, but these are often negative early in the disease and repeat testing is required. Specific micro-immunofluorescence (MIF) is the method of choice; the two rickettsial species are not routinely distinguishable serologically, but this is unimportant as far as treatment is concerned. Although still widely used in South Africa, the Weil-Felix agglutination test is now regarded as obsolete as it is neither sensitive nor specific. Direct detection by MIF or PCR of skin biopsies is possible but these techniques are not recommended for routine use. In most patients the white blood cell count remains within the normal range with neutrophilia being typical. In complicated disease neutropenia and thrombocytopenia may be noted.

Q fever is a protean illness with a wide differential diagnosis, encompassing causes of atypical pneumonia, hepatitis, encephalitis, carditis, osteomyelitis, miscarriage, and fever of unknown origin. Rarely, Q fever may present as multi-organ failure and resemble bacterial septicaemia. It is likely that many cases are undiagnosed; a history of animal contact is important to elicit or exclude in making a clinical assessment.

Laboratory diagnosis rests on serological tests (preferably MIF) to show rising titres. Antibodies (IgM and IgG) to phase II antigens dominate in acute infections; high levels of IgG and IgA phase I antibodies, equalling or exceeding phase II IgG antibody titres, indicate chronic disease.[34] The Weil-Felix test is negative in Q fever.

Treatment

Chemotherapy for TBF has never been well evaluated in large-scale clinical trials. Although the disease will resolve spontaneously in some patients, it can be severe in many patients and avoidance of therapeutic delay with antibiotic therapy is recommended to prevent complications. Tetracycline-group antibiotics are the treatment of choice for TBF, with doxycycline superior to other formulations. For adults, doxycycline 100 mg bd for 5 - 7 days is recommended although the duration of therapy is not well studied and shorter courses may be adequate.[36] Doxycycline is highly effective and a clinical response with symptom relief and fever defervescence can be expected within 48 hours. Failure of response within this period should suggest the possibility of another diagnosis.

Chloramphenicol and the 4-fluorinated quinolones show activity *in vitro*, but clinical data on efficacy are limited.[37] However a 4-fluorinated quinolone such as ciprofloxacin, or chloramphenicol, may be the only available options in critically ill patients who are unable to tolerate oral medication, as parenteral formulations of tetracycline are unavailable in South Africa. Erythromycin has poor efficacy and there are insufficient clinical data to recommend the new macrolides such as clarithromycin and azithromycin.[37,38] As TBF can be life-threatening in patients of any age group, treatment with the most effective agent, doxycycline, is recommended therapy for all patients. Therefore doxycycline should be strongly considered at least for initial therapy even in children under 8 years of age, and pregnant women. In these groups of patients an initial 2 days of doxycycline should be given followed by 3 - 5 days of a macrolide to complete the therapeutic course. Limited data support the use of steroids in patients with fulminant TBF, or disease complicated by acute respiratory distress. Most of the experience of steroids in rickettsial disease can be extrapolated from use in patients with complicated Rocky Mountain spotted fever.[38]

The treatment of choice for Q fever pneumonia is a tetracycline. Alternative agents used include the 4-fluorinated quinolones and chloramphenicol. Erythromycin has been shown to be less effective,[38] but newer macrolides may be useful. Co-trimoxazole is recommended for children and pregnant women.[34] Prolonged antimicrobial treatment for Q fever endocarditis is required. Doxycycline, in combination with ciprofloxacin or rifampicin, for at least 2 years should be considered.[38] The combination of hydroxychloroquine (to alkalinise phagolysosomes) and doxycycline for 18 months has been effective.[34]

References

1. Gear JHS. The rickettsial diseases of southern Africa. *S Afr J Clin Sci* 1954; 5: 158-175.
2. Raoult D, Fournier P-E, Eremeeva M, *et al*. Naming of rickettsiae and rickettsial diseases. *Ann NY Acad Sci* 2005; 1063: 1-12.
3. Conor A, Bruch A. Une fièvre éruptive observée en Tunisie. *Bull Soc Path Exot* 1910; 8: 492-496.
4. McNaught JG. A note on two cases of paratyphoid fever in which a new variety of paratyphoid bacillus was found in the blood. *J R Army Med Corps* 1908; 10: 171-174.
5. McNaught JG. Paratyphoid fevers in South Africa. *J R Army Med Corps* 1911; 16: 505-514.
6. Sant' Anna JF. On a disease in man following tick-bites and occurring in Lourenço Marques. *Parasitology* 1911; 4: 87-88.
7. Nuttall GHF. On symptoms following tick-bites in man. *Parasitology* 1911; 4: 89-93.
8. Troup JM, Pijper A. Tick-bite fever in southern Africa. *Lancet* 1931; 2: 1183-1186.
9. Pijper A, Crocker CG. Rickettsioses of South Africa. *S Afr Med J* 1938; 12: 613-630.
10. Gear JHS. South African typhus. *S Afr J Med Sci* 1938; 3: 134-160.
11. Kelly P, Matthewman L, Beati L, *et al*. African tick bite fever: a new spotted fever group rickettsiosis under an old name. *Lancet* 1992; 340: 982-983.
12. Raoult D, Fournier PE, Fenollar F, *et al*. *Rickettsia africae*, a tick-borne pathogen in travelers to sub-Saharan Africa. *N Engl J Med* 2001; 344: 1504-1510.
13. Jensenius M, Fournier P-E, Kelly P, Myrvang B, Raoult D. African tick bite fever. *Lancet Infect Dis* 2003; 3: 557-564.
14. Cohen GL, Blumberg LS, Karstaedt AS. Tick bite fever in black South Africans – a rare disease? *J Infect* 1996; 32: 235-237.
15. Ndip LM, Bouyer DH, Travassos Da Rosa APA, Titanji VPK, Tesh RB, Walker DH. Acute spotted fever rickettsiosis among febrile patients, Cameroon. *Emerg Infect Dis* 2004; 10: 432-437.
16. Kelly PJ, Mason PR, Matthewman LA, Raoult D. Seroepidemiology of spotted fever group rickettsial infections in humans in Zimbabwe. *J Trop Med Hyg* 1991; 94: 304-309.
17. Jensenius M, Fournier P-E, Vene S, *et al*. African tick bite fever in travelers to rural sub-equatorial Africa. *Clin Infect Dis* 2003; 36: 1411-1417.
18. Pretorius A-M, Birtles RJ. *Rickettsia aeschlimannii*: a new pathogenic spotted fever group rickettsia, South Africa. *Emerg Infect Dis* 2002; 8: 874.
19. Pretorius A-M, Birtles RJ. *Rickettsia mongolotimonae* infection in South Africa. *Emerg Infect Dis* 2004; 10: 125-126.
20. Kelly PJ. *Rickettsia africae* in the West Indies. *Emerg Infect Dis* 2006; 12: 224-226.
21. Derrick E. Q fever, a new fever entity: clinical features, diagnosis and laboratory investigation. *Med J Aust* 1937; 2: 281-299.
22. Marrie TJ, Raoult D. Q fever – a review and issues for the next century. *Int J Antimicrob Agents* 1997; 8: 145-161.
23. Gear JHS, Wolstenholme B, Miller B, Sher R, Schneider J. Q fever in South Africa. In: Gear JHS, ed. *Medicine in a Tropical Environment*. Cape Town: AA Balkema, 1977: 471-478.
24. Kelly PJ, Matthewman LA, Mason PR, Raoult D. Q fever in Zimbabwe. A review of the disease and the results of a serosurvey of humans, cattle, goats and dogs. *S Afr Med J* 1993; 83: 21-25.
25. Matthewman L, Kelly P, Hayter D, *et al*. Exposure of cats in southern Africa to *Coxiella burnetii*, the agent of Q fever. *Eur J Epidemiol* 1997; 13: 477-479.
26. Olano JP. Rickettsial infections. *Ann NY Acad Sci* 2005; 1063: 187-196.
27. Walker DH, Valbuena GA, Olano JP. Pathogenic mechanisms of diseases caused by *Rickettsia*. *Ann NY Acad Sci* 2003; 990: 1-11.
28. Raoult D, Marrie TJ, Mege JL. Natural history and pathophysiology of Q fever. *Lancet Infect Dis* 2005; 5: 219-226.
29. Isaäcson M, Hale MJ. Infections caused by rickettsiae and rickettsia-like organisms and bartonellosis. In: Doerr W, Siefert G, eds. *Tropical Pathology*. Berlin: Springer-Verlag, 1995: 264-276.
30. Jackson Y, Chappuis F, Loutan L. African tick-bite fever: four cases among Swiss travelers returning from South Africa. *J Travel Med* 2004; 11: 225-230.
31. Bellini C, Monti M, Potin M, Dalle Ave A, Bille J, Greub G. Cardiac involvement in a patient with clinical and serological evidence of African tick-bite fever. *BMC Infect Dis* 2005; 5: 90.
32. Jensenius M, Fournier PE, Fladby T, *et al*. Sub-acute neuropathy in patients with African tick bite fever. *Scand J Infect Dis* 2006; 38: 114-118.
33. Raoult D, Levy PY, Dupont HT, *et al*. Q fever and HIV infection. *AIDS* 1993; 7: 81-86.
34. Parker NR, Barralet JH, Bell AM. Q fever. *Lancet* 2006; 367: 679-688.
35. Rolain JM, Gouriet F, Brouqui P, *et al*. Concomitant or consecutive infection with *Coxiella burnetii* and tickborne diseases. *Clin Infect Dis* 2005; 40: 82-88.
36. Raoult D, Drancourt M. Antimicrobial therapy of rickettsial diseases. *Antimicrob Agents Chemother* 1991; 35: 2457-2462.
37. Miller GB, Gear JHS. Treatment of tick-bite fever with erythromycin. *S Afr Med J* 1984; 66: 694-697
38. Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia: Elsevier Churchill Livingstone, 2005: 2284-2301.