Fatal tick bite fever cases

Three cases of fatal tick bite fever (TBF) have been investigated by the NICD in recent months.

Case 1
A 40-year-old female horse-back rider from Schweizer-Reneke in North West Province reported a tick bite before falling ill, and noted an eschar on her back. She complained of severe headache and fever which progressively worsened, and was admitted to a Bloemfontein hospital with signs suggestive of encephalitis; radiological imaging revealed a cerebral infarct with bleeding. Initial laboratory test results for TBF were confounding, and she died two weeks later. The patient was an organ donor, and a definitive diagnosis became critical to facilitate the organ donation process. Given the history of a tick bite together with the fulminant nature of the illness, Crimean-Congo haemorrhagic fever (CCHF) infection had to be excluded. All tests for CCHF were negative, but testing for rickettsia IgG and IgM using indirect immunofluorescence was positive, confirming the clinical and circumstantial evidence supporting the diagnosis of TBF.

Case 2
A 50-year-old female from Brackenfell, Western Cape Province, reported going on a picnic at the Breede River before she fell ill. The patient was admitted to hospital with fever (>40°C), headache and decreased level of consciousness. No typical eschar was found on examination, although the presence of a small, raised erythematous lesion on her leg was noted. Abnormal laboratory test results included moderately elevated hepatic transaminases and thrombocytopenia. The patient died approximately two weeks later. Laboratory investigation for CCHF was negative, but TBF was confirmed by serology and PCR.

Case 3
A 63-year-old farmer in Wellington, Western Cape Province, presented with an acute febrile illness and reported nausea and malaise. He was initially treated in hospital overnight for a suspected allergic reaction, but his condition deteriorated rapidly. He developed haematemesis, became hypotensive and experienced three cardiac arrests. A black eschar was found on his hairline, suggesting the possibility of TBF. Intravenous ciprofloxacin was commenced as he was unable to tolerate oral doxycycline, but he demised within 24 hours of admission to hospital. CCHF was considered as a possible diagnosis, given the exposure to ticks, geographical location, and clinical presentation of the patient. However, the likelihood of CCHF was anticipated to be low, since liver transaminases were only marginally elevated, thrombocytopenia was moderate, and the presence of a typical eschar supported a diagnosis of TBF. Nevertheless, the patient was isolated and barrier-nursed, and specimens were submitted to the NICD for CCHF investigation. Reverse transcription PCR and CCHF-specific IgG and IgM serology were all negative. A diagnosis of TBF was confirmed by indirect immunfluorescence assay which was positive for anti-rickettsia IgM and IgG.

Discussion
Severe TBF disease with complications (including encephalitis, bleeding, DIC, hepatorenal failure, ARDS, digital gangrene and myocarditis) may mimic other diseases, including CCHF, meningococcal septicaemia, or fulminant Gram-negative septicaemia. Healthcare workers should be aware that TBF must feature in the differential diagnosis of acute febrile illness in at-risk persons. Risk factors include travel in Southern Africa, hiking in rural areas, living on small holdings in peri-urban areas, and living/working on farms. However, even persons living in urban areas who are exposed to ticks in the home setting may potentially be at risk. An eschar, often located by finding tender regional lymphadenopathy, together with fever and headache should prompt treatment with doxycycline. A maculopapular rash, typically including the palms and soles, may be noted in infections with *Rickettsia conorii* but is generally absent in *Rickettsia africae* infections. The classical triad of TBF (fever, eschar and rash) occurs in 50-75% of cases, but eschars may not be typical and the rash may be variable. Doxycyline is the treatment of choice, generally administered for 5-7 days; it is highly effective and a clinical response with symptom relief and defervescence can be expected within 48 hours. Since TBF can potentially be severe and life-threatening, all patients should initially be treated with doxycycline since it is the most effective treatment. For pregnant women and children <8 years of age, an initial 48 hours of therapy with doxycycline should be given followed by a macrolide such as clarithromycin or azithromycin for 3-5 days to complete the course of therapy. In critically-ill patients unable to tolerate oral doxycycline, intravenous ciprofloxacin is the only treatment option since intravenous doxycycline is not available in South Africa. Limited data and extrapolation from experience with Rocky Mountain spotted fever supports the use of corticosteroids in patients with fulminant TBF or TBF disease

complicated by ARDS.

TBF is a clinical diagnosis, and a patient presenting with an acute febrile illness, eschar and rash should receive prompt doxycycline treatment. Laboratory confirmation of TBF in the first week of illness is challenging and results may be misleading given the low sensitivity of both PCR and serology. Antibody seroconversion usually occurs from day 10 of illness. PCR can be performed on buffy coat preparations (obtained from EDTA whole blood), and eschar swabs/biopsies. The historical Weil-Felix test is obsolete given its unacceptably low sensitivity and specificity.

Source: Centre for Emerging and Zoonotic Diseases and Division of Public Health Surveillance and Response, NICD/NHLS