

## CRIMEAN-CONGO HAEMORRHAGIC FEVER AND TICK-BITE FEVER IN SOUTH AFRICA, 2012 - 2014

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### Introduction

Crimean-Congo haemorrhagic fever (CCHF) virus (*Bunyaviridae: Nairovirus*) and *Rickettsia africae* (*Rickettsiales: Rickettsiaceae*), the aetiological agent of African tick-bite fever (TBF), are medically important, endemic tick-borne pathogens in South Africa.

Crimean-Congo haemorrhagic fever virus is typically transmitted by the so-called “bont poot” ticks, *Hyalomma rufipes* and *H. truncatum*, while TBF is transmitted by “bont ticks”, *Amblyomma variegatum* and *A. hebraeum*.<sup>1</sup> Ticks become infected by feeding on the blood of a viraemic or rickettsaemic vertebrate animal. Infection in these tick species is chronic and spans the lifetime of the vector, and ticks appear to be both vector and reservoir for these pathogens.

Although the two pathogens should be considered in the differential diagnosis of tick-acquired fevers, they are geographically aligned to the distribution of their tick vectors. The *Hyalomma* species, and therefore CCHF virus, occur in the more arid parts of South Africa, particularly on the inland plateau. On the other hand, the *Amblyomma* species and *R. africae* tend to be associated with the subtropical region of the Lowveld, below the Drakensberg Escarpment. Exposure to CCHF virus or *R. africae* may also occur outside of the endemic regions when tick vectors have been introduced through the movement of cattle and sheep, or the translocation of wildlife. These ticks tend to be two- and three-host ticks, where the larval, nymphal and adult stages feed on different hosts. Humans tend to be targeted by the immature tick stages. However, where tick specimens associated with CCHF cases have been submitted for

testing, these have usually been adult male hyalommas.

The natural cycle of CCHF virus includes transovarial, trans-stadial and non-viraemic transmission among ticks, and a tick-vertebrate-tick cycle involving a variety of wild and domestic animals. Transovarial transmission occurs through the infection of tick eggs, allowing the virus or rickettsia to be transmitted to the next generation without the necessity of blood-feeding. Trans-stadial transmission involves survival of the pathogen from larval to nymphal to adult stage ticks as each stage moults into the next. “Non-viraemic” transmission occurs between infected and uninfected ticks during co-feeding on the same host.<sup>2</sup>

*Hyalomma* ticks feed on a variety of domestic ruminants (sheep, goats, and cattle) as well as wild herbivores, hares, hedgehogs and certain rodents. Although CCHF virus infection in animals is generally subclinical, it generates viraemia levels capable of supporting virus transmission to uninfected ticks.<sup>3</sup> Many birds are resistant to infection, and ostriches appear to be the most susceptible of the birds.<sup>3</sup> Results from serological surveys conducted in Africa and Eurasia indicate extensive circulation of the virus in livestock and wild vertebrates.<sup>4</sup>

The natural transmission cycle of *R. africae* is less well understood, apart from the tick-human link. *Amblyomma* ticks are also ectoparasitic on a wide variety of domestic and wild mammals (both large and small) and are also more likely to parasitize ground-frequenting birds than *Hyalomma* species. Although these hosts may not serve

as reservoirs for *R. africae*, they do still represent a source of tick vectors.

*Rickettsia conorii* is an introduced tick-borne pathogen that is typically confined to urban areas. This rickettsial organism is responsible for causing the classical Mediterranean spotted fever (fièvre boutonneuse) and is transmitted by the kennel (brown dog) tick, *Rhipicephalus sanguineus*, to dogs and humans. It is believed to have been introduced to southern Africa from North Africa and the Mediterranean Region.<sup>5</sup>

### Epidemiology of tick-bite infections

#### Transmission to humans

Humans acquire CCHF virus infection from tick bites, squashing of infected ticks or from contact with infected blood or other tissues of livestock or human patients. The initial fever develops into severe disease, frequently followed by a haemorrhagic state with necrotic hepatitis resulting in a mortality rate of up to 30%.<sup>6,7</sup> CCHF virus transmission is rare in the general human population and transmission by ticks most frequently occurs among farmers or field workers. Human-to-human transmission and outbreaks of CCHF can also occur through close physical contact with highly viraemic people (nosocomial transmission). The risk of transmission of rickettsial infection from human and animal hosts is reduced owing to low-level rickettsaemia that only lasts for a short period, especially in human hosts.<sup>6</sup> The tick-to-human transmission of rickettsiae is common in areas such as the Kruger National Park, where people are exposed at a young age as a consequence of outdoor activities.

#### Prevalence in humans

The rates of tick-bite and CCHF infections in humans are highly influenced by the prevalence of tick vectors. *Amblyomma*, *Hyalomma* and *Rhipicephalus* ticks are common in livestock areas. *Amblyomma variegatum* and *A. hebraeum* feed readily on humans<sup>8,9</sup> and are commonly infected with *R. africae* (16%–75%) in widely

separated regions of Africa.<sup>10-12</sup> For example, *Rickettsia* species were detected by polymerase-chain-reaction (PCR) in 12.5% (17/136) of ticks from cattle and in 3.1% (22/700) of ticks from the vegetation in a survey in Nigeria. In this study the estimated infection rate of cattle in positive herds ranged from 15.4% to 50%, with an average of 20.6%.<sup>13</sup> Sero-surveys conducted on humans in areas of endemicity have shown up to 100% antibody prevalence.<sup>6, 14-16</sup>

Serological evidence of human infection with CCHF is uncommon, despite the widespread and high prevalence of CCHF virus antibodies amongst sheep, cattle and hares throughout South Africa. A serosurveillance study conducted in the 1980s found high antibody prevalence to CCHF virus in cattle herds in the interior of the country, with over 90% in some herds, while the seroprevalence was less than 4% in cattle in the coastal region between Cape Town and East London. Only 17/1109 (1.5%) of human residents on 55 farms had antibodies to CCHF, while no veterinary staff engaged in farm animal practice were CCHF seropositive.<sup>17</sup> Other rural studies in South Africa revealed that human infection with CCHF virus is uncommon (12.6/1,000, 1.3%). 12.7% of young animals on farms with human cases were antibody positive compared with 5.8% on those farms with no known human cases.<sup>18</sup>

A more recent survey to establish the seroprevalence of CCHF virus in the North West Province was carried out on 109 extensive cattle farms in 2002. A total of 8 505 cattle sera were collected from these farms and tested by means of an IgG sandwich ELISA. All 109 farms tested positive for the presence of antibodies to CCHF virus. Individual herd antibody prevalence ranged from 31.9% to 100% of tested animals (mean=80%). No linear relationship between dipping frequency and herd prevalence could be established (unpublished data). The North West Province, South Africa, has produced eighteen laboratory confirmed human cases of CCHF

since 1981, and ranks third following the Northern Cape and Free State Provinces.

#### CCHF and TBF cases confirmed for the period 2012-2014 in South Africa

The Centre for Emerging and Zoonotic Diseases (CEZD) of the National Institute for Communicable Diseases (NICD) functions as a national reference laboratory for the diagnosis of arboviruses and bacterial and viral haemorrhagic fevers (BHF and VHF), including CCHF, the most significant VHF in South

Africa, and the rickettsioses, as part of the differential diagnosis of VHF. Rickettsia tests are also provided by a number of private laboratories in the country.

The CCHF figures reported here represent the national figures available for South Africa. Twenty-one VHF cases were investigated for CCHF by CEZD during 2012. No CCHF cases were confirmed, but three cases had serological evidence of recent or current rickettsial infection. In 2013, five cases of CCHF and two cases of TBF were diagnosed out of thirty-five tick-bite disease-

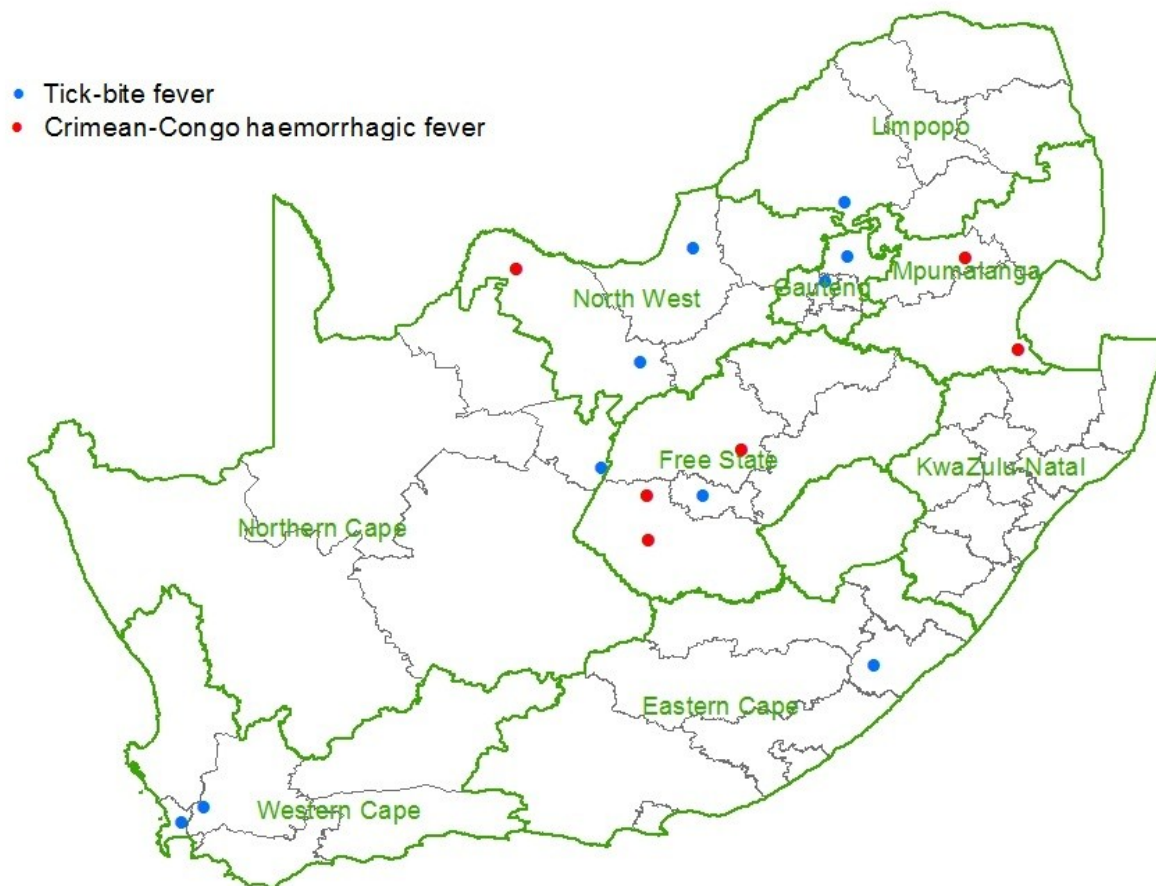


Figure 1: Geographical localities of confirmed Crimean-Congo haemorrhagic fever (CCHF) and tick-bite fever (TBF) cases in South Africa, 2012-2014.

During the 2012 to 2014 period, the six confirmed CCHF cases originated in the Free State (n=3), North-West (n=1) and Mpumalanga (n=2) Provinces. The ten TBF cases originated from seven out of nine SA provinces:

Free State (n=1), North-West (n=2), Northern Cape (n=1), Eastern Cape (n=1), Western Cape (n=2), Limpopo (n=1) and Gauteng (n=2).

Table 1: Characteristics Crimean-Congo haemorrhagic fever (CCHF) or African tick-bite fever (ATBF) cases from South Africa, 2012-2014.

Variable	Patients with CCHF (N=6)	Patients with ATBF (N=10)	Patients without CCHF, ATBF (N=58)	Relative Risk for patients with 1) CCHF, 2) ATBF versus without CCHF, ATBF	
				RR (95% CI)	P-value
Mean age, years (range)	43 (36-47)	49 (23-75)	42(3-79)	1) N/A 2) N/A	
Male	83% (5/6)	50% (5/10)	66% (38/58)	1) 1.27(0.85-1.90) 2) 0.76(0.40-1.46)	0.7 0.5
Tick bite/eschar	67% (4/6)	88% (7/8)	27% (11/41)	1) 2.48(1.16-5.31) 2) 3.26(1.85-5.76)	0.07 0.002*
Farming/Hunting	100% (6/6)	63% (5/8)	39% (16/41)	1) 2.56(1.75-3.76) 2) 1.60(0.83-3.10)	0.007* 0.3
Fatal outcome	0/6	40% (4/10)	24% (12/50)**	1) N/A 2) 1.67(0.67-4.12)	0.4

\*RR significant at  $p < 0.05$  by Fisher's exact 2-tailed test.

\*\*Low rate of follow-up for an ill patient without confirmed CCHF or TBF

Amongst the few cases where case histories were obtainable, tick bite was commonly reported for CCHF cases (67%, 4/6), as was eschar in TBF cases (88%, 7/8) (table 1). All suspected cases associated with working with animals or living on a farm tested positive for exposure to CCHF virus. Persons with CCHF infection were more likely to have farming or hunting occupations than suspected patients without laboratory confirmation of CCHF or TBF (RR: 2.56,  $p=0.007$ ).

The severity and mortality rate of TBF cases varies greatly according to the tick vector and the geographic area. African tick bite fever in Sub-Saharan Africa is a relatively mild infection with a documented case fatality rate of 3%.<sup>19</sup> CCHF has a higher case-fatality rate (CFR) because the disease does not resolve easily and carries a greater risk of complications if not diagnosed and treated timeously.<sup>20</sup> In South Africa, CCHF CFR is 24% as estimated from 194 cases confirmed since 1981. Mortality is higher during nosocomial outbreaks. Patient survival is improved after an illness lasting more than 5 days. No case-fatalities were reported amongst the six

CCHF cases documented for the 2012-2014 period. However, four of the TBF cases in 2014 were fatal.

#### Clinical diagnosis and treatment of tick-bite infections

Ticks may attach to numerous parts of the human body but are most frequently found in hidden areas around the head and neck and in the groin. Tick bites usually do not cause pain and immature stages are frequently not detected because of their small size. Tick-bite marks are difficult to find; inoculation eschars and regional lymphadenitis on medical examination of patients are usually the first indicators of exposure to CCHF or rickettsioses.<sup>14,21</sup> Rickettsial diseases share symptoms with a broad range of febrile illnesses including fever, myalgia and headache, and thus clinical diagnosis can be difficult. Some African tick bite fever cases present with a distinct vesicular cutaneous rash, but this is not a general feature of *R. africae* infection.<sup>14,21</sup> Many people who experience flu-like symptoms will not present for medical evaluation, which suggests that tick-bite fever is underreported. CCHF may be easier to diagnose

clinically, especially if a patient reaches the haemorrhagic phase. Late-phase infection manifests as a petechial or purpurral rash, with extensive subcutaneous bleeding or other bleeding of the gastro-intestinal tract, uterus, urinary tract, and respiratory mucosae (table 2).

The fever preceding this phase is usually more elevated and other flulike symptoms - myalgia, dizziness, diarrhoea, vomiting, nausea and conjunctivitis - are

more severe.<sup>20</sup> The incubation period for CCHF ranges from 3-7 days and for TBF from 6-7 days.<sup>20, 22</sup>

The rickettsiae are amenable to treatment with doxycycline, preferably administered as soon as symptoms (fever and sensitive, swollen lymph node/s) appear. The CCHF patient may respond to supportive clinical management and antiviral treatment with ribavirin when administered shortly after exposure to the virus.

Table 2: Clinical features reported of confirmed Crimean-Congo haemorrhagic fever (CCHF) and African Tick bite fever (ATBF) cases from South Africa, 2012-2014.

Tick bite infection symptoms	CCHF (6)	ATBF (10)	Tick bite infection symptoms	CCHF (6)	ATBF (10)
<b>Signs Symptoms documented</b>	<b>6</b>	<b>9</b>	<b>Signs Symptoms documented</b>	<b>6</b>	<b>9</b>
Fever	6	5	Venipuncture bleeding	1	1
Thrombocytopenia	5	6	Nausea		1
Elevated hepatic transaminases	4	4	Vomiting		1
Headache	3	5	Malaise		1
Myalgia	3	3	Arthralgia		1
Petechial rash	3		Weakness		1
Non-specified rash	2	2	Maculopapular rash		2
Haematemesis	2	1	Jaundice/hepatitis		2
Leukopenia	2	1	Encephalopathy		2
Epistaxis	1		Raised C-reactive protein		2
Gum bleeding	1		Intracranial haemorrhage		1
Conjunctivitis	1		Leucocytosis		2
Sore throat/pharyngitis	1				

### Laboratory diagnosis of tick-bite infections

Serological testing remains the most commonly used diagnostic technique for rickettsial infections in Africa. The NICD performs immuno-fluorescent assays because of better sensitivity and specificity compared to the outdated Weil and Felix test. However, cross-reactions between anti-*connorii* and anti-*africae* antibodies are common. The NICD is also equipped for molecular detection and identification by polymerase chain reaction (PCR). Bio-security measures are in

place to do isolation and cell culture and these remain the gold standard in the diagnosis of rickettsias. Early TBF diagnosis is often based solely on symptoms and case history. This is because laboratory confirmation in the first week of illness is challenging due to low sensitivity of both PCR and serology.

The management of CCHF cases crucially depends on rapid diagnosis and isolation of the patient. Reverse transcription polymerase chain reaction (RT-PCR) and

serological testing by either IFA or ELISA provide rapid results. Patients with fatal disease, as well as patients in the first few days of illness, do not usually develop a measurable antibody response and so diagnosis in these individuals is achieved by virus isolation or RNA detection in blood samples. Virus isolation by cell culture is the gold standard. Tests on patient samples present a high biohazard risk and are only conducted in the high biocontainment facility of the CEZD.

### Conclusion

Limited epidemiological data exists on tick-borne infections in South Africa. The data presented here are therefore a retrospective analysis of suspected cases for

which specimens were submitted for laboratory testing. More integrated surveillance studies should be conducted in human, animal and tick populations to identify risk factors for these diseases, so as to provide information on the proportion of people that previously have been infected with CCHF or TBF, and to indicate the range of symptomatic responses these infections can cause in disease endemic areas and in groups potentially at risk of infection.

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