Review

Rickettsia africae: identifying gaps in the current knowledge on vector-pathogen-host interactions

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Abstract

Rickettsia africae is a bacterium of zoonotic importance, which causes African tick bite fever (ATBF) in humans. This pathogen is transmitted by ticks of the genus Amblyomma, with Amblyomma hebraeum and Amblyomma variegatum being the major vectors. Tick species other than the above-mentioned have also been reported to carry R. africae DNA. There is scarcity of information on the epidemiology of this pathogen, yet several cases have been recorded in foreign travellers who visited endemic areas, especially southern Africa. The disease has rarely been described in people from endemic regions. The aim of this study was to discuss the information that is currently available on the epidemiology of R. africae, highlighting the gaps in this field. Furthermore, ATBF cases, clinical signs and the locations where the cases occurred are also listed in this review.

Key words: Rickettsia africae; African tick bite fever; Amblyomma hebraeum.

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Introduction

Rickettsia africae is a bacterium that was first reported as a species 24 years ago [1]. It is mainly transmitted by African Amblyomma tick species, causing African tick bite fever (ATBF) in humans; mostly in tourists visiting southern Africa [2].

This paper reviews R. africae from the epidemiological perspective, looking at the occurrence of ATBF among individuals from presumed naïve populations never exposed to African Amblyomma bites, and those from endemic regions, where the populations are commonly exposed to R. africae challenge, the potential vectors of this disease in Africa and other continents, and the possible role of mammalian hosts as reservoirs.

Methodology

Review design

Articles with information related to ATBF, R. africae, tick bite fever, South African tick bite fever, and data on the seroprevalence of ATBF were gathered. Articles written in any language other than English were not included, except for those of historical importance. Searches had no restriction on the research period. Data on ATBF cases reported worldwide were also gathered and ATBF cases included in this study (Table 1) were only those reported from 2004 onwards. This review does not include six ATBF reports which were published from 1996 to 2003, however, two references supporting the cases reported during this time interval were included in this paper. The cases reported in this paper are sufficient in terms of geographic representation and individuals involved and period of cases.

Materials

The databases Medline, Science Direct, PubMed, Google scholar and Google.com were used to perform the searches for publications on the topic. Some articles were retrieved from citations and reference lists in papers on the related topic. The first search date was the 10th of June 2018 and the last search on google.com was conducted on the 6th of June 2019; the last search date for other databases was the 14th of June 2019.

Study selection

Duplicates were removed and articles were selected if their titles and abstracts were related to ATBF, R. africae, tick bite fever, South African tick bite fever or ATBF seroprevalence.
Data collection

Articles reporting ATBF cases were included in this review, irrespective of geographical region. In addition, papers focussing on the diagnosis of ATBF and detection of *R. africae* were also included. Among the articles reporting ATBF cases, only those published from 2004 onwards were considered. Unusual clinical signs of ATBF in humans, which are symptoms not usually reported to be associated with ATBF, and the detection of *R. africae* in tick species other than *Amblyomma* were also noted. Additionally, *Amblyomma* tick hosts are discussed since they are likely to play a major role in the epidemiology of *R. africae*.

Results

Data on cases of ATBF in presumed naïve populations and those from endemic regions were collected. For all articles reporting case studies, the following data were tabulated: the year of publication, age of affected persons, gender, nationality, country visited (if any), purpose of the visit to the area where the infection was acquired, the clinical signs presented in each case and the diagnostic method used (Table 1). Unusual clinical signs of ATBF in humans and the detection of *R. africae* in tick species other than *Amblyomma* were also included (Table 2).

From 36 ATBF reports, 57 recorded ATBF patients were included in this study. This disease was also found to occur as clustered cases since more than one person would be affected. This review includes seven reports of clustered ATBF cases. Out of the 57 patients included in this study, 40 had information on sex and age. Between the age zero to 29 years there were two females and six males, between 30-60 years, there were 11 females and 13 males, between 61 and 90 years, three were females and five were males. Out of the 57 cases mentioned, only three were reported from the endemic areas, two from South Africa and one from Zimbabwe and the rest were from international travellers who had visited African countries for various activities as indicated on Table 1.

The most common ATBF clinical signs were headache, fever, eschars, rash, lymphadenopathy, myalgia, chills, malaise and arthralgia. Some unusual clinical signs were also reported in some patients and these were; myocarditis, pericarditis, conjunctivitis, decreased vision, floaters, panuveitis, and neurological signs such as feecal incontinence, urinary retention, hyperesthesia, depressed and significant irritability. ATBF was also found to have neurological complications in elderly patients.

Table 1. Some of the African tick bite fever cases that have been published worldwide from 2004 to June 2019 (See methodology for selection criteria).

| Year | Country of origin | No. of people | Sex and age (years) | Country of travel | Purpose of travel | Clinical presentation | Diagnostic techniques | References |
|------|-------------------|---------------|---------------------|-------------------|-------------------|----------------------|----------------------|------------|
| 1992 | Zimbabwe          | 1             | F (36)              | None, Indigenous person | No history of travel | Eschar, fever, severe headache lymphadenopathy, | PCR and restriction endonuclease fragment length polymorphism with oligonucleotide primer pairs for 190kDa, 120kDa, Restriction endonucleases Rsa1, Pol1 | Kelly et al. [11] |
| 2004 | United States     | 1             | M (62)              | Zambia and Malawi   | Safari and sight seeing | Eschar, lymphangitis, fever, regional lymphadenopathy | Serology | Uslan [39] |
| 2004 | Switzerland       | 4             | M (55)              | South Africa        | Safari             | Myalgia, headache, neck pain, nausea | Serology | Jackson et al. [40] |
| 2004 | Switzerland       | 2             | F (55)              | South Africa and Swaziland | Campaign | Fever, rash, lymphadenitis, asthma, chest pain, myocarditis, pericarditis fever, rash, myalgia, arthralgia, headache, lymphadenitis | Serology | Bellini et al. [41] |
| 2005 | United States     | 1             | M (13)              | Zimbabwe            | Safari             | Fever, malaise, myalgia, headache, eschars, lymphadenopathy | Blood culture and blood smears negative, diagnosis based on symptoms | Snape and Pollard [42] |
| 2006 | United States     | 1             | F (48)              | Zimbabwe            | Mission trip, History of visiting game farm | Fever, malaise, eschars, lymphadenopathy, anorexia, dizziness | Culture on eschars followed by PCR, Serology | Owen et al. [43] |
| 2008 | France            | 8             | M and F             | South Africa        | Safari             | Fever (6 cases), chills (?), headaches (5), myalgia, asthena, anorexia, weight loss, eschars (5), rash (?), conjunctivitis (4), lymphadenitis (2) | Culture on eschars followed by PCR, Serology | Roech et al. [44] |
| 2008 | South Africa      | 1             | F (3)               | None, Indigenous    | General visit      | Fever, headache, regional lymphadenopathy, eschar on scalp, maculopapular rash | † | Frean et al. [9] |
| 2008 | Germany           | 1             | F (60)              | South Africa        | †                  | Fever, chills, vesiculat exanthema | Serology | Schuer et al. [45] |
| 2009 | France            | 1             | F (43)              | South Africa        | Safari             | Fever, fatigue, headache, muscle pain, | Serology, Western blotting | Comigny et al. [46] |
| Year | Country of origin | No. of people | Sex and age (years) | Country of travel | Purpose of travel | Clinical presentation | Diagnostic techniques | References |
|------|------------------|---------------|---------------------|-------------------|-------------------|----------------------|----------------------|------------|
| 2009 | Taiwan           | 1             | F (62)              | South Africa      | Safari and leisure | Mild fever, eschars, skin nodules, erythematous papules | Serology, Nested PCR (Suicide PCR using primers; AF3F, AF3R, AF4F, AF4R followed by AF3F, AF3R, AF6F, AF6R) | Tsai et al. [47] |
| 2009 | Germany          | 1             | F†                  | South Africa      | Safari            | Fever, headache, malaise | Serology, Pan-Rickettsia real time PCR and sequencing of gltA | Tappe et al. [48] |
| 2010 | Poland           | 1             | M (51)              | South Africa      | Safari            | Fever, chills, eschar, generalised cutaneous rash | PCR | Tomasiewicz et al. [49] |
| 2012 | United States    | 1             | F (52)              | Zambia and Botswana | Work and safari | Fever, eschar, mild headache, non-productive cough, chills, sweating | Clinical signs | Schwartz et al. [50] |
| 2013 | Poland           | 1             | M (45)              | South Africa      | Safari            | Fever, generalised muscle pain and weakness, eschars, maculopapular rash on trunk and arms, lymphadenopathy | Serology, Rickettsia-specific PCR – gltA, ompA, 17kDA genes, Sequencing of gltA and 17kDA genes | Chmielowski et al. [51] |
| 2013 | Germany          | 1             | M (47)              | South Africa      | Vacation          | Fever, eschar, regional lymphadenopathy, headache, malaise | IFA, PCR, laboratory tests - elevated Coagulate protein | Antal et al. [52] |
| 2014 | United States    | 1             | M (76)              | South Africa      | Hunting           | Headache, muscle weakness, fever, eschars on leg, regional lymphadenopathy | Routine histology and culture done on FNA of affected LN | Yankura and Lofreda [53] |
| 2014 | Italy            | 1             | F (40)              | Zimbabwe          | Work (mission hospital-medical doctor) | Fever, eschar on l. leg, fatigue, neurological syndrome with severe pain of left leg, urinary retention, facial incontinence | PCR | Zammarchi et al. [36] |
| 2015 | Netherlands      | 2             | M (53)              | South Africa      | Safari            | Fever, eschar, regional lymphadenopathy, maculopapular rash on extremities, shoulder pains radiating to neck (myalgias) | History and clinical signs | Cox and Visser [54] |
| 2015 | United States    | 1             | F (51)              | South Africa      | Safari            | Fever, eschar, regional lymphadenopathy | PCR | Hohaty and Hebert [55] |
| 2015 | France           | 1             | M (66)              | South Africa      |                  | Headache, myalgia, odynophagia, fever, eschars | PCR | Franon and Mancoumdia [56] |
| 2015 | United States    | 1             | M (65)              | India and South Africa | Safari and general visit | Fever, night sweats, myalgia, arthralgias, generalised stiffness, eschar on lateral hip, ulcers on neck | Serology, Western blotting, PCR and sequencing – gltA, 17kDA, ompA, 23S rRNA | Binder and Gupta [57] |
| 2015 | Sweden           | 1             | M (56)              | South Africa      | Safari            | Fever, eschar on thorax | Serology, Western blotting, PCR and sequencing – gltA, 17kDA, ompA, 23S rRNA | Nilsson et al. [38] |
| 2016 | United States    | 1             | M (30)              | Zimbabwe          | Visit rural and urban | Fever, malaise, painful swelling in the groin region, regional lymphadenopathy | Serology, PCR | Hauer et al. [58] |
| 2016 | Canada           | 1             | F(67)               | Africa            | Safari            | Fever, malaise, eschar on elbow, rash, depressed vision, floaters, pan-avulcsis and retinitis | Serology | Duval and Merril [37] |
| 2016 | Austria          | 1             | F (30)              | Tanzania          | Work              | Fever, chills, headache, general malaise, eschar myalgia, lymphadenopathy | PCR and sequencing – gltA, ompA, 16S rRNA, 23S-5S intergenic spacer | Harrison et al. [59] |
| 2016 | Slovenia         | 1             | M (29)              | Uganda            |                  | Eschar, regional lymphadenopathy, fever | Serology, PCR and sequencing – gltA gene | Biogovic et al. [60] |
| 2017 | Spain            | 3             | M (7)               | South Africa      | Safari            | Fever, headache, myalgia, generalised erythematous papules, lymphadenopathy | Serology, R. africae PCR on blood sample | Albizuri et al. [61] |
| 2017 | Spain            | 3             | M (8)               | South Africa      | Safari            | Fever, headache, myalgia, multiple eschar, regional lymphadenopathy | Serology | Serology, PCR – gltA, ompA, the specific Spotted Fever Group gene D, Sequencing ompA gene | Armitano et al. [62] |
| 2017 | Argentina        | 3             | M†                  | South Africa      | Game hunting      | All three of them presented with arthralgias, regional lymphaditis, fever, chills, eschars | Serology, PCR – gltA, ompA, 17kDA, 23S rRNA, 5S intergenic spacer | Serology, PCR – gltA, ompA, the specific Spotted Fever Group gene D, Sequencing ompA gene | Serology, PCR – gltA, ompA, the specific Spotted Fever Group gene D, Sequencing ompA gene | Armitano et al. [62] |
| 2017 | Canada           | 1             | M (51)              | South Africa      | Safari            | Headache, diffuse myalgia and arthralgias, chills, fever, fatigue, reduced appetite, eschar | Serology, PCR and sequencing - ompA | Liou and Carr [63] |
| 2017 | Germany          | 1             | M (73)              | South Africa      | Safari            | General malaise, fever, regional lymphadenopathy, eschars on legs, arms and trunk | Serology | Menzer et al. [64] |
| 2017 | United States    | 1             | M (53)              | South Africa      | Safari            | Eschar, general malaise, myalgia, regional lymphadenopathy | PCR and sequencing - ompA | Siadat et al. [65] |
| 2018 | Netherlands      | 1             | F (61)              | South Africa      | Safari            | Fever, headache, eschar, diarrhoea, regional lymphadenopathy | Eschar cultured, PCR and sequencing - gltA, ompA, 17kDA | Feigen et al. [66] |
| 2018 | Brazil           | 1             | M (32)              | South Africa      | Safari            | Fever, headache, eschar, diarrhoea, regional lymphadenopathy | Eschar cultured, PCR and sequencing - gltA, ompA, 17kDA | Angerami et al. [67] |

†: Unknown data; ‡: New African Tick Bite Fever feature and they are in bold; M: Male; F: Female; The cases which are in bold report ATBF in patients from ATBF endemic areas.

References

[59] Harrison et al.
[60] Biogovic et al.
[61] Albizuri et al.
[62] Armitano et al.
[63] Liou and Carr
[64] Menzer et al.
[65] Siadat et al.
[66] Feigen et al.
[67] Angerami et al.
Discussion

Historical background

Fever associated to tick bites was first reported in southern Africa in 1911 by Nuttall, who named it "tick bite fever" (TFB) [3,4]. The disease was also termed Boutonneuse fever by Conor and Bruch after its first discovery in Tunisia in 1910 [5].

In the 1930s, Pijper noted differences between the clinical signs of the disease that was termed 'TFB', identified in southern Africa in 1911, and those of Boutonneuse fever, discovered in North Africa in 1910 [6–8]. In addition, he noted differences both in the epidemiology and clinical severity of the two diseases. Boutonneuse fever had more severe clinical signs as compared to TBF. Pijper’s peers refuted his findings and attributed the differences in the severity of the two diseases to the age differences between the people who were affected [1,9]. However, Pijper’s observations are currently accepted [10]. In fact Pijper possibly isolated the causative agent of ATBF in the 1930’s and demonstrated that it was different from R. conorii by cross-protection assays (Pijper 1936, Arch.Inst. Pasteur Tunis 25, 388-401 as cited by Fournier et al. (1998) [8].

The discovery of R. africae

Amblyomma hebraeum tick bites were found to be associated with TBF in Africa in the 1990s, and many cases were reported in southern Zimbabwe [1]. This was consistent with Pijper’s report, in which he indicated that A. hebraeum ticks were predominant in southern Rhodesia (now Zimbabwe) [7].

In 1992, a 36-year-old Zimbabwean woman presented at a hospital in Chiredzi, a small town in south-east Zimbabwe, with fever, headache, regional lymphadenopathy and inoculation eschar, but no cutaneous rash. A blood sample was collected from the patient on the fifth day after presentation. DNA was extracted and restriction fragment length polymorphism (RFLP) were performed [11]. The isolate was found to be the same as those collected from A. hebraeum from several regions in Zimbabwe [1], as well as a spotted fever group (SFG) rickettsia isolate from Ethiopia [12]. This new isolate was named Rickettsia africae in

Table 2. Tick species, other than Amblyomma, in Africa in which R. africae DNA was found.

| Tick                     | Host                        | Country             | Method                        | Reference        |
|--------------------------|-----------------------------|---------------------|-------------------------------|------------------|
| Haemaphysalis elliptica  | Dogs                        | South Africa        | PCR and Sequencing            | Kolo et al. [69] |
| Haemaphysalis paralaeichi| Dogs and goats              | Guinea              | PCR and sequencing            | Mediannikov et al. [70] |
| Hyalomma dromedarii      | Camels                      | Algeria             | PCR and Sequencing            | Kernif et al. [71] |
| Hyalomma dromedarii      | Camels and cattle           | Egypt               | PCR and sequencing            | Abdel-shafy et al. [72] |
| Hyalomma impeltatum       | Camels and cattle           | Egypt               | PCR and sequencing            | Abdel-shafy et al. [72] |
| Hyalomma marginatum       | Camels and cattle           | Egypt               | PCR and sequencing            | Mediannikov et al. [70] |
| Hyalomma rufipes          | Cattle                      | Guinea              | PCR and sequencing            | Sambou et al. [73] |
| Hyalomma truncatum        | Cattle, sheep, goats        | Kenya               | PCR and sequencing            | Mutai et al. [74] |
| Rhipicephalus (Boophilus) annulatus | Cattle, sheep, goats | Guinea              | PCR and sequencing            | Mediannikov et al. [70] |
| Rhipicephalus (Boophilus) decoloratus | Cattle, sheep, dogs, cats | Ethiopia            | PCR and sequencing            | Hornok et al. [75] |
| Rhipicephalus (Boophilus) geigyi | Cattle                        | Ethiopia            | PCR and sequencing            | Kumsa et al. [76] |
| Rhipicephalus (Boophilus) microplus | Cattle                        | Guinea              | PCR and sequencing            | Mediannikov et al. [70] |
| Rhipicephalus appendiculatus | Cattle and goats            | Union of the Comoros| PCR and sequencing            | Yssouf et al. [78] |
| Rhipicephalus evertsi     | Cattle, sheep, goats, donkeys, horses | Senegal            | PCR and sequencing            | Mediannikov et al. [79] |
| Rhipicephalus pulchellus  | Cattle, sheep, goats        | Kenya               | PCR and sequencing            | Mutai et al. [74] |
| Rhipicephalus            | Dogs                        | Nigeria             | PCR and sequencing            | Ogo et al. [77]  |
| Rhipicephalus compositus  | Cattle                      | Kenya               | PCR and sequencing            | Macaluso et al. [80] |
1996, after it was proved that two different Rickettsiae species were causing two different rickettsial diseases in southern Africa [1]. Tick bite fever, caused by R. africae, was found to be associated with a history of travel to grasslands and game parks, whereas, Boutonneuse fever, caused by R. conorii, was associated with a history of contact with the dog ticks, Rhipicephalus sanguineus, Rhipicephalus simus, and Haemaphysalis leachi [11] in peri-urban or peri-domestic settings. Humans infected with this pathogen showed severe clinical signs, which were associated with high mortality rates [1].

**Biology and characteristics of R. africace**

*Rickettsia africace* is an obligate intracellular, Gram-negative coccobacillus [13]. It was proved by electron microscopy that this bacterium can be found within the cytoplasm of host cells and has an outer slime layer as well as a tri-lamellar cell wall. The cell wall of *R. africace* contains lipopolysaccharide antigens. These are highly immunogenic and responsible for extensive cross-reactivity with other species of SFG rickettsiae [13]. Species-specific protein antigens are found in the high-molecular-weight rickettsial outer membrane protein A (rOmpA) and B (rOmpB). The rOmpA protein seems to be specific to SFG rickettsiae [14]. Most species of the SFG rickettsiae have been characterized by SDS-polyacrylamide gel electrophoresis (PAGE), Western blot and PCR-RFLP analysis [14]. The bacterium cannot be cultured in cell-free media. However, it can grow in the yolk sacs of developing chicken embryos, and in cell cultures [1].

**Detection of R. africace**

The methods commonly used to detect and confirm the presence of *R. africace* in tissue are PCR and sequencing respectively. A quantitative PCR (qPCR) targeting the citrate synthase gene (*gltA*) is the most frequently used *Rickettsia* genus-screening assay [15]. After screening, *gltA* positive samples are usually tested in a conventional PCR (cPCR) targeting the *ompA* gene of SFG rickettsiae [15] and more recently, a qPCR targeting the *ITS* gene was developed for the same purpose [16]. Sequencing is the only method currently available to identify SFG rickettsiae at species level.

**Amblyomma vectors of R. africace**

It is generally accepted that the ticks that transmit *R. africace* in Africa belong to the genus *Amblyomma* of the family Ixodidae (hard ticks), with *A. variegatum* and *A. hebraeum* being the main vectors [13]. *A. hebraeum* is mainly distributed in southern Africa and *A. variegatum* in West, Central and eastern Africa, as well as in the eastern Caribbean [17]. *A. variegatum* is also present in some parts of southern Africa where it extends into Zambia, north eastern Botswana, the Caprivi Strip of Namibia, Angola, north western Zimbabwe and central and northern Mozambique. It also occurs in Madagascar and several Indian Ocean islands [17].

*Amblyomma hebraeum* tick species are considered to be the main vector of *R. africace* in South Africa [13]. The infestation of humans by this species and infection with *R. africace* is relatively common due to the wide distribution of the tick vector in rural areas of the country. *Rickettsia africace* infection rates of up to 100% have been detected by PCR and sequencing in *Amblyomma* ticks from endemic areas [18,19]. The *A. hebraeum* and *A. variegatum* tick species are three-host ticks and all active developmental stages (larvae, nymphs and adults) have been proved to be potential vectors of *Rickettsia* [20,21]. Studies performed by Kelly (1991) and Mason and Socolovschi *et al.* (2009), reported that these tick vectors can maintain *R. africace* through transovarial and trans-stadial transmission through two generations [22,23].

*Rickettsia africace* DNA was also detected in *Amblyomma lepidum*, *Amblyomma gemma*, *Amblyomma cohaerens*, and *Amblyomma compressum* in Sudan, Djibouti [23], and in the Somali region of Ethiopia [16,19]. Furthermore, *R. africace* was also detected in *Amblyomma loculosum*, a tick species that is usually known for infesting marine birds in tropical islands [24,25]. *R. africace* DNA was found in *Amblyomma ovale* ticks collected from dogs in Nicaragua, Central America, in 2013. This was the first report on *R. africace* in the American continent [26].

Given the documented distribution of *R. africace* among African *Amblyomma* species, it is reasonable to infer that all African *Amblyomma* species could be competent vectors of this pathogen. However, this assumption should be confirmed. In this context, it is worth mentioning the recent finding of the intergration of *R. africace* chromosome in the nuclear genome of *A. variegatum*, which can have major implications on detection specificity of *R. africace* in *Amblyomma* species [27].

Different studies conducted between 2003 and 2016 in the African continent (Table 2) report other tick species in which *R. africace* DNA was found such tick species belong to *Haemaphysalis*, *Hyalomma* and *Rhipicephalus* genera. However, the available data does not provide direct evidence of vector competence for any of these vectors. All the studies that had such
reports indicated that the ticks were collected from vertebrate hosts hence the \textit{R. africae} DNA detected could have been from the blood meals they had on the hosts and not due to infection of the tick tissues with the \textit{Rickettsia}. Therefore, there is a need for further investigation on \textit{R. africae} vector competence. In addition to the above mentioned ticks, \textit{R. africae} was also detected in fleas collected from migratory birds [28].

\textbf{Mammalian hosts as reservoirs of \textit{R. africae}}

On the African continent, \textit{A. hebraeum} and \textit{A. variegatum}, the main vectors for \textit{R. africae}, have a wide host range that includes domestic and wild species [29]. These vectors show a marked preference for large animal species and thus prefer cattle to other domestic species such as goats, sheep and donkeys. Among wild species, buffalo, eland, giraffe and kudu are preferred [13]. These wild ungulates are of major importance to the ecology of the \textit{Rickettsia} species in areas where domestic animals are dippied intensively or where these animals are absent [13]. The adult stages of these ticks feed on wild ungulates. The hosts for larvae and nymphs are the same as those for adult ticks, however, they can also feed on lizards, small mammals and ground-feeding birds [30]. Humans are accidental hosts for these ticks and legs are the usual attachment sites for them. The ticks can also crawl on the skin and may be found attaching to the groin or axilla, where there is moisture [13]. These ticks respond to stimuli like carbon dioxide, ammonia, humidity, aromatic chemicals, airborne vibration and body temperature, all of which are strongly associated with their predilection sites on their hosts [31].

Ticks require blood meals for their continued development, reproduction and survival. Cattle play an important role in the ecology of \textit{R. africae} by maintaining tick populations [18]. Serological surveys in cattle, conducted in Zimbabwe, using the immunofluorescence antibody (IFA) assay, showed that 80-100\% of animals have antibodies against SFG rickettsiae [32,33]. In spite of the serological evidence indicating exposure to \textit{R. africae}, no clinical signs associated to infection with \textit{R. africae} have been reported in animals.

Experimental studies on the pathogenesis of SFG rickettsiae in Zimbabwe suggest the maintenance of the pathogen in cattle [32]. All sero-negative cattle (n = 8), experimentally infected with rickettsia organisms isolated from \textit{A. hebraeum} ticks and cultured in Vero cells, were found to be positive on IFAT after three days post-infection. To determine rickettsiemia in these cattle, sero-negative guinea pigs were inoculated with blood from the experimentally infected cattle. All guinea pigs sero-converted, indicating that these cattle were rickettsemic for at least 32 days post-infection [32]. This constituted the first experimental evidence of the possible role of cattle as reservoirs for \textit{R. africae}. However, it is worth pointing out that this suggestion is solely based on the sero-conversion in cattle and guinea pigs, which should be regarded with caution considering the low specificity of \textit{Rickettsiae} serological assays. To confirm bovine hosts as reservoirs of \textit{R. africae}, experiments using DNA-based methods should be performed. The uncertainty of the role of cattle as \textit{R. africae} reservoirs is further corroborated by a study conducted in Kenya, where no rickettsemia was detected in cattle, sheep and goats, while 92.6\% of \textit{A. variegatum} recovered from the same animals tested positive \textit{R. africae} DNA [18]. The scarcity of studies on \textit{R. africae} diversity and the role of cattle or any other mammalian hosts as \textit{R. africae} reservoirs has been recognised as a major gap in the understanding of \textit{R. africae} epidemiology in the African continent.

Transovarial transmission of \textit{R. africae} is well documented [22]. However, there are no studies on the efficiency of transovarial transmission for several generations in \textit{Amblyomma} ticks. This is of great importance since it can provide conclusive evidence on whether \textit{R. africae} can be maintained in its vector without the need for mammalian hosts as reservoirs.

\textbf{ATBF presentation in different populations}

Cases of ATBF in humans usually occur in clusters. This is because of the feeding habits of \textit{Amblyomma} ticks; they hide in their microhabitats and attack hosts as they appear. This is especially noticed in tourists visiting endemic areas [34]. ATBF presents with flu-like symptoms with fever, nausea, fatigue, headache and myalgia. Most of the cases in Table 1 were associated with these common ATBF clinical signs. The disease is usually self-limiting. However, in the elderly and immunocompromised individuals, it can be more severe. Some ATBF cases in Table 1 were associated with complications such as chronic fatigue, reactive arthritis, encephalitis, myocarditis and cellulitis have also been reported, but mostly in the elderly [35]. Complicated ATBF in a 40-year-old Italian traveller returning from Zimbabwe was reported to have painful sacral syndrome characterised by severe pain on the leg, urinary retention and faecal incontinence and rectal tenesmus and these were attributed to be due to immune mediated mechanisms [36]. Duval and Merrill (2016), also reported a
complicated case of ATBF where retinitis was the main symptom in a 67 year old lady from Canada [37]. Tick bite sites appear as either single or multiple inoculation eschars [35]. The typical inoculation eschar associated with ATBF consists of a central black crust surrounded by a red halo, occurring as a result of inflammation [9]. Acute cases have been reported in travellers from Europe and America after they visited southern African countries [38]. A report by Frean et al. (1998), indicated an estimated infection rate of 4-5% in foreign travellers visiting South Africa [9]. Clinical signs usually appear after they return to their country of origin since the incubation period of ATBF is five to ten days [24]. ATBF is a self-limiting disease hence many people may be affected and they do not visit hospitals for treatment. The disease can also be misdiagnosed for other diseases which present with fever like malaria and typhoid. This could be the case in many African countries where proper diagnostic laboratories and facilities are lacking. Difficulty in diagnosing the disease in the indigenous population could be also attributed to pigmented skin since it could be very difficult to notice the inoculation eschars hence such pathognomonic features of the disease are easily missed [21]. Although underreporting and misdiagnosis of ATBF can contribute to the underestimation of the disease in populations from endemic regions, the epidemiology of this infection in African rural areas strongly suggests early exposure leading to the establishment of endemic stability in these populations [22]. Furthermore, there are limited publications on the seroprevalence of R. africae in the rural population in areas where the tick vector exists [13], which makes it difficult to determine the status of immunity to this pathogen at population level.

Conclusions

Rickettsiae africaco, transmitted by A. variegatum and A. hebraeum, was definitively associated with ATBF in 1996. Since then, the organism’s DNA has been detected in other Amblyomma species, both in the African and American continents. Furthermore, R. africae DNA has also been detected in tick species other than Amblyomma. Further studies on the vector competence of other tick genera for this pathogen should be performed in order to fully clarify the dynamics of R. africae infection in different ecological niches. Literature on the role of mammalian hosts is scarce and contradictory. Moreover, in spite of the confirmation of transovarial transmission, the capacity for vertical transmission for several generations has yet to be fully elucidated.

A striking feature of the clinical presentation of ATBF is the marked difference between humans from presumed naïve populations and those from endemic regions since almost all of the reported ATBF cases reported worldwide were from international travellers after trips to ATBF endemic areas. In order to confirm whether endemcity is the cause of the sporadic occurrence of clinical signs from humans in rural areas of Africa, structured serological surveys including different age cohorts should be conducted.

This review highlights significant gaps in R. africaco research, which, if addressed, will result in the better comprehension of ATBF epidemiology.

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References

1. Kelly PJ, Beati L, Mason PR, Matthewman LA, Roux V, Raoult D (1996) Rickettsia africaco sp. nov., the etiological agent of African tick bite fever. Int J Syst Bacteriol 46: 611–614.
2. Jensenius M, Fournier PE, Kelly P, Myrvang B, Raoult D (2003) African tick bite fever. Lancet Infect Dis 3: 557–564.
3. Nuttall GHF (1911) On symptoms following tick-bites in man. Parasitology 4: 89-93.
4. Troup JM, Pijper A (1931) Tick-bite fever in Southern Africa. Lancet 2: 1183-1186.
5. Conor A, Bruch A (1910) An eruptive fever observed in Tunisia. Bull Soc Path Exot 3: 492–496. [Article in French].
6. Pijper A (1934) Tick-bite fever: a clinical lecture. S Afr Med J 8: 551-556.
7. Pijper A, Crocker CG (1938) Rickettsioses of South Africa. S Afr Med J 12: 613-630.
8. Fournier PE, Roux V, Caumes E, Donzel M, Raoult D (1998) Outbreak of Rickettsia africaco infections in participants of an adventure race in South Africa. Clin Infect Dis 27: 316–323.
9. Frean, Blumberg, Ogunbanjo (2008) Tick bite fever in South Africa. SAFP 50: 33-35.
10. Frean, J, Grayson W (2019) South African tick bite fever: an overview. Dermatopathology 6: 70–76.
11. Kelly P, Matthewman L, Beati L, Raoult D, Mason P, Dreary M, Makombe R (1992) African tick-bite fever: A new spotted fever group rickettsiosis under an old name. Lancet 340: 982-983.
12. Burgdorfer W, Ormsbee RA, Schmidt ML, Hooogstraal H (1973) A search for the epidemic typhus agent in Ethiopian ticks. Bull World Health Organ 48: 563–569.
13. Jensenius M, Fournier PE, Vene S, Hoel T, Hasle G, Henriksen AZ, Hellum KB, Raoult D, Myrvang B, Norwegian African tick bite fever study group (2003) African tick bite fever in travelers to rural Sub-Equatorial Africa. Clin Infect Dis 36: 1411–1417.
14. Roux V, Fournier P (1996) Differentiation of spotted fever group rickettsiae by sequencing and analysis of restriction fragment length polymorphism of PCR-amplified DNA of the gene encoding the protein rOmpA. J Clin Microbiol 34: 2058–2065.

15. Stenos J, Graves SR, Unsworth NB (2005) A highly sensitive and specific real-time PCR assay for the detection of spotted fever and typhus group rickettsiae. Am J Trop Med Hyg 73: 1083–1085.

16. Kumsa B, Socolovschi C, Raoul D, Parola P (2019) Spotted fever group rickettsiae in ixodid ticks in Oromia, Ethiopia.Ticks Tick Borne Dis 6: 8–15.

17. Walker AR, Bouattour A (2003) Ticks of domestic animals in Africa: A guide to identification of species. Edinburgh: Bioscience Rep. 3:210.

18. Maina AN, Jiang J, Omulo SA, Cutler SJ, Ade F, Ogola E, Feikin DR, Njenga MK, Cleaveland S, Mpoke S, Ng’ang’a Z (2014) High prevalence of Rickettsia africae variants in Amblyomma variegatum ticks from domestic mammals in rural western Kenya: implications for human health. Vector Borne Zoonotic Dis 14: 693–702.

19. Tomassone L, Meneghi D De, Adakal H, Rodighiero P, Pressi G, Grego E (2016) Detection of Rickettsia aeschlimannii and Rickettsia africae in ixodid ticks from Burkina Faso and Somalian region of Ethiopia by new real-time PCR assays. Ticks Tick Borne Dis 7: 1082–1088.

20. Kelly PJ, Mason PR (1991) Transmission of a spotted fever group rickettsia by Amblyomma hebraeum (Acari: Ixodidae). J Med Entomol 28: 598–600.

21. Kelly PJ (2006) Rickettsia africae in the West Indies. Emerg Infect Dis 12: 224–226.

22. Kelly PJ, Mason PR (1991) Tick-bite fever in Zimbabwe. Survey of antibodies to Rickettsia conorii in man and dogs, and of Rickettsia-like organisms in dog ticks. South African Med J 80: 233–236.

23. Socolovschi C, Huynh TP, Davoust B, Gomez J, Raoul D, Parola P (2009) Transovarial and trans-stadial transmission of Rickettsiae africanae in Amblyomma variegatum ticks. Clin Microbiol Infect 15: 317–318.

24. Eldin C, Mediamnikov O, Davoust B, Cabre O, Barré N, Raoul D, Parola P (2011) Emergence of Rickettsia africanae, Oceania. Emerg. Infect. Dis 17: 100–102.

25. Dietrich M, Lebarbanchon, Camille Jaeger A, Le Rouzi C, Matthieu B, Lagace E, McCoy KD, Pascalis H, Le Corre M, Dellagi K, Tortosa P (2014) Rickettsia spp. in seabird ticks from western Indian Ocean islands, 2011–2012. Emerg Infect Dis 20: 838–846.

26. Vogel H, Foley J, Fiorello CV. (2018) Rickettsia africanae and novel rickettsial strain in Amblyomma spp ticks, Nicaragua, 2013. Emerg Infect Dis 24: 385–387.

27. Darby AC, Al-Khafaji AM, Whitehead M, Hartley CS, Robinson G, Armstrong SD, Belaviskaia AY, Bah GS, Githaka N, Bell-Sakyi L, Makepeace B (2019) Amblyomma variegatum, vector of African tick-bite fever, contains an integrated Rickettsia africanae chromosome in its nuclear genome. Am J Trop Med Hyg 101: 211.

28. Sekeyová Z, Mediamnikov O, Roux V, Subramanian G, Špitálská E, Kristofik J, Darolová A, Raoul D (2012) Identification of Rickettsia africanae and Wolbachia sp. in Ceratophyllum garei fleas from passerine birds migrated from Africa. Vector Borne Zoonotic Dis 12: 539-543.

29. Halajian A, Palomar AM, Portillo A, Heyne H, Romero L, Oteo JA (2018) Detection of zoonotic agents and a new Rickettsia strain in ticks from donkeys from South Africa: implications for travel medicine. Travel Med Infect Dis 26: 43–50.

30. Socolovschi C, Huynh TP, Davoust B, Gomez J, Raoul D, Parola P (2009) Transovarial and trans-stadial transmission of Rickettsiae africanae in Amblyomma variegatum ticks. Clin Microbiol Infect 15: 317–318.

31. Althaus F, Greub G, Raoul D, Genton B (2010) 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 14: 274–276.

32. Kelly PJ, Mason PR, Manning T, Slater S (1991) Role of cattle in the epidemiology of tick-bite fever in Zimbabwe. J Clin Microbiol 29: 256–259.

33. Parola P, Davoust B, Raoul D (2005) Tick- and flea-borne rickettsial emerging zoonoses. Vet Res 36: 469–492.

34. Caruso G, Zasio C, Guzzo F, Granata C, Mondardini V, Guerra E, Macri E, Benedetti P (2002) Outbreak of African tick-bite fever in six Italian tourists returning from South Africa. Eur J Clin Microbiol Infect Dis 21: 133–136.

35. Nilsson K, Wallöménus K, Rundlöf-nygren P, Strömåsdahl S (2017) African tick bite fever in returning Swedish travellers. Report of two cases and aspects of diagnostics. Infect Ecol Epidemiol 07: 1343081.

36. Zammarchi L, Farese A, Trota M, Amantini A, Raoul D, Bartoloni A (2014) Rickettsia africanae infection complicated with painful sacral syndrome in an Italian traveller returning from Zimbabwe. Int J Infect Dis 29: 194–196.

37. Duval RM, Merrill PTM (2016) Spotted fever group rickettsia retinitis in a traveler to Africa. Retin Cases Br Reports 10: 89–92.

38. Parola P (2006) Rickettsioses in sub-Saharan Africa. Ann N Y Acad Sci 1078: 42–47.

39. Uslan DZ, Sia IG (2004) African tick bite fever: Mayo Clin Proc 79: 1007.

40. Jackson Y, Chappuis F, Loutan L (2004) African tick-bite fever: four cases among Swiss travelers returning from South Africa. J Travel Med 11: 225–228.

41. Bellini C, Monti M, Potin M, Dalle Ave A, Bille J, Greub G (2005) Cardiac involvement in a patient with clinical and serological evidence of African tick-bite fever. BMC Infect Dis 5: 1-6.

42. Snape MD, Pollard AJ (2006) African tick bite fever. Lancet Infect Dis 6: 750.

43. Owen CE, Bahrami S, Malone JC, Callen JP, Kulp-shorten CL (2006) African tick bite fever. Arch. Dermatol 142: 1312–1314.

44. Roch N, Epaulard O, Pelloux I, Pavese P, Brion J, Raoul D, Maurin M (2008) African tick bite fever in elderly patients: 8 cases in French tourists returning from South Africa. Clin Infect Dis 47: e28–e35.

45. Schuster J, Tantcheva-Poor I, Wickenhauser C, Chemnitz JM, Hunzelmann N, Krieg T, Hartmann K (2008) African tick bite fever - Papulovesicular exanthem with fever after staying in South Africa. JDDG 6:379-381.

46. Consigny PH, Ina S, Fraitag S, Rolain JM, Buffet P (2009) Unusual location of an inoculation lesion in a traveler with African tick-bite fever returning from South Africa. J Travel Med 16: 439–440.

47. Tsai KH, Lu HY, Huang JH, Fournier PE, Mediamnikov O, Raoul D, Shu PY (2009) African tick bite fever in a Taiwanese traveler returning from South Africa: molecular and serologic studies. Am J Trop Med Hyg 81: 735–739.
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