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Clinical, epidemiological, and laboratory features of *Rickettsia africae* infection, African tick-bite fever: A systematic review

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SUMMARY

African tick-bite fever (ATBF), caused by *Rickettsia africae*, is the main tick-borne rickettsiosis and the second most frequent cause of fever after malaria in travelers returning from sub-Saharan Africa. General descriptions on ATBF were made in the first two decades after recognized as a new infectious entity, and since then, many authors have contributed to the knowledge of the disease by reporting clinical cases in scientific literature. We developed a systematic review that evaluated all available evidence in the literature regarding clinical, epidemiological, and laboratory features of confirmed *R. africae* rickettsiosis cases. We followed the recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guide. A total of 48 scientific publications (108 confirmed cases) were analyzed in order to extract data for developing this review. Overall, our results show that *R. africae* rickettsiosis is more frequent in males in the age group of 18-64 years, more than 80% of the cases occurred in European travelers, South Africa was the country where most infections were acquired, and almost 40% of cases occurred in clusters. Clinically, more than 80% of the cases had fever and eschar (55% developed multiple eschars), rash was present in less than the half of cases, and lymphangitis was not a common sign (11%). Headache, myalgia and regional lymphadenopathy were predominant nonspecific clinical manifestation (mean of 60%, 49% and 51%, respectively). Our results show that at least 70% of *R. africae* cases had altered laboratory parameters, most often showing an increase in transaminases and C-reactive protein. Tetracycline-class antibiotics, as monotherapy, were used in most (>90%) of the patients. Overall, only 4% of cases had complications, 12% required hospitalization, and there was a 100% rate of clinical recovery.

Keywords: Rickettsia, *Rickettsia africae*, African tick-bite fever, Systematic Review.

INTRODUCTION

International travel to Africa, mostly because of tourism, has been increasing during recent years, becoming an important risk factor for the emergence and re-emergence of some local infectious diseases in people from non-African countries [1]. African tick-bite fever (ATBF) is a spotted fever group (SFG) rickettsiosis caused by *Rickettsia africae* for which the importance has increased as the main tick-borne rickettsiosis and the second most frequent cause of fever after malaria in travelers returning from sub-Saharan Africa [2].
Before the official description of *R. africae* as a new species of the SFG, ATBF was confused with Mediterranean spotted fever, caused by *Rickettsia*

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conorii, but clinical and epidemiological differences related to complications and geographic areas of these infections had already been noted [3]. In 1992 *R. africae* was isolated from the blood of a Zimbabwean febrile patient who presented an erythematous lesion behind the right ear in the site of a tick-bite [4]. Polymerase chain reaction (PCR) and restriction endonuclease fragment length polymorphism proved that *R. africae* was distinct from other SFG rickettsiae including *R. conorii*, but identical to isolates from *Amblyomma hebraeum* and *Amblyomma variegatum*, ticks species collected in Zimbabwe and Ethiopia, respectively [4-6]. Thus, in 1996 *R. africae* was officially recognized as the etiologic agent of ATBF [7].

A. variegatum and *A. hebraeum* are considered the main vectors and reservoirs of *R. africae* since infection is maintained through transovarial and transstadial transmission in these ticks [7]. The distributions of *A. variegatum* and *A. hebraeum* are geographically different; the former is distributed through rural areas of central, east and west Africa, and in the eastern Caribbean islands, and the latter is circumscribed to southern Africa [8, 9]. These *Amblyomma* species have an aggressive behavior, and patients are often bitten by multiple infected ticks simultaneously, mainly on the lower extremities [8].

In ATBF endemic areas, native individuals are generally infected at a young age and usually do not seek medical attention because symptoms are not clearly evident (e.g., inoculation eschar is difficult to see in pigmented skin, disease might be mild or subclinical at a young age) [8]. For travelers, popular wildlife activities including hunting, hiking and safari in endemic areas are considered risk factors, as well as travelling during rainy season from November to April, the peak of tick activity [8-10].

Diagnosis of ATBF can be established by isolation and molecular techniques on blood or eschar sample (including eschar swab and skin biopsy), the eschar being more useful for diagnostic confirmation [10, 11]. Other diagnostic methods include immunofluorescence assay (IFA), western blotting (WB), and cross-adsorption tests, alone or combined, since some patients are not always positive for all the methods [11].

General descriptions of clinical, epidemiological and laboratory features of ATBF were made in the first two decades after the disease was recognized as a new infectious entity, and since then many authors have contributed to the knowledge of the disease by reporting clinical cases in the scientific literature; nevertheless, to our knowledge, no systematic review related to *R. africae* infection (ATBF) has been published. Thus, the aim of this systematic review is to evaluate all available evidence in the literature regarding the clinical, epidemiological, and laboratory features of *R. africae* rickettsiosis.

METHODS

Search strategy and selection criteria

We followed the recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide all the steps of this review. Searching for scientific literature was carried out on March 18, 2021, in four scientific literature databases: PubMed MEDLINE, EMBASE, Scopus and BVS. Separate searches using the terms ["*Rickettsia africae*" AND "case"] and ["African tick bite fever" AND "case"] were performed in all the four databases. The references of all the articles were extracted and collected in a library created in "EndNoteX8" program combining both searches. Once the reference list was created, elimination of duplicate articles was carried out using the automatic tool of the program. Results of the procedure provided list of potentially useful articles for analysis and selection.

We reviewed all the literature managed in the eligible list in order to choose those that would be part of this review. Since other pathogenic SFG rickettsiae are endemic to Africa (the main ATBF endemic region), including *R. conorii*, *R. aeschlimannii*, *R. sibirica mongolitimonae*, and *R. monacensis*, we only included confirmed infections with *R. africae* in order to guarantee the accuracy in our analysis [12]. Thus, the inclusion criteria were case reports, clinical cases, and other papers written in English or Spanish language in which there was a report of confirmed clinical case in humans associated with *R. africae* infection. Those publications that did not fulfill inclusion criteria were excluded.

Data extraction

We (CRSR, ÁAFM) independently screened the titles and abstracts to identify relevant reports. Possible disagreements were resolved through group discussion. Data were extracted from the included studies and tabulated in an Excel form. For each article, we extracted information related to clinical manifestations of all confirmed cases. Ad-

ditionally, we also performed the data extraction related to the country of the patient's origin, country of travel where the infection was presumed to have occurred, sex and age of the reported patients, history of cluster infection, history of tick exposure, hematological and biochemical laboratory findings, complications, diagnostic test used including sample type, antibiotic therapy used, need for hospitalization and clinical outcome.

Definitions

Based on publications of Raoult and Cherry, we defined a confirmed case of *R. africae* infection as a clinically and epidemiologically compatible illness with isolation of *R. africae* in cell culture and/or sequence identification of *R. africae* using PCR-positive products from DNA extracted from clinical samples (blood, serum, eschar, eschar swab, skin biopsy) and/or a Western blot result that showed *R. africae* specific antibodies and/or cross adsorption studies demonstrating homologous antibodies directed against *R. africae* [10, 11].

RESULTS

Scientific literature search

Figure 1 summarizes our search procedure. Using the terms ["*Rickettsia africae*" AND "case"], 44, 79, 106 and 93 publications were found in the PubMed MEDLINE, EMBASE, Scopus and BVS databases respectively, giving a total of 322 scientific publications found. The terms ["African tick bite fever" AND "case"] yielded 72, 94, 116 and 117 publications, respectively, in the same databases, giving a total of 399 scientific publications. Combining both search procedures, a total of 721 publications were extracted and loaded in the "EndNoteX8" program in order to eliminate duplicate publications, giving a total of 255 eligible scientific publications.

Literature selection

From the eligible list of 255 scientific publications, we selected 46 as they fulfilled the inclusion criteria indicated in "Selection criteria". In parallel, we added 2 additional publications that were not found in the databases following our search procedure, which fulfilled the inclusion criteria and reported *R. africae* infection cases confirmed by PCR on blood samples and on eschar biopsy [13, 14]. Thus, a total of 48 scientific publications were analyzed in order to extract data for this review [4, 13-59].

Demographic and epidemiological data

A total of 108 clinical cases were reported in the 48 analyzed publications [4, 13-59]. Data related

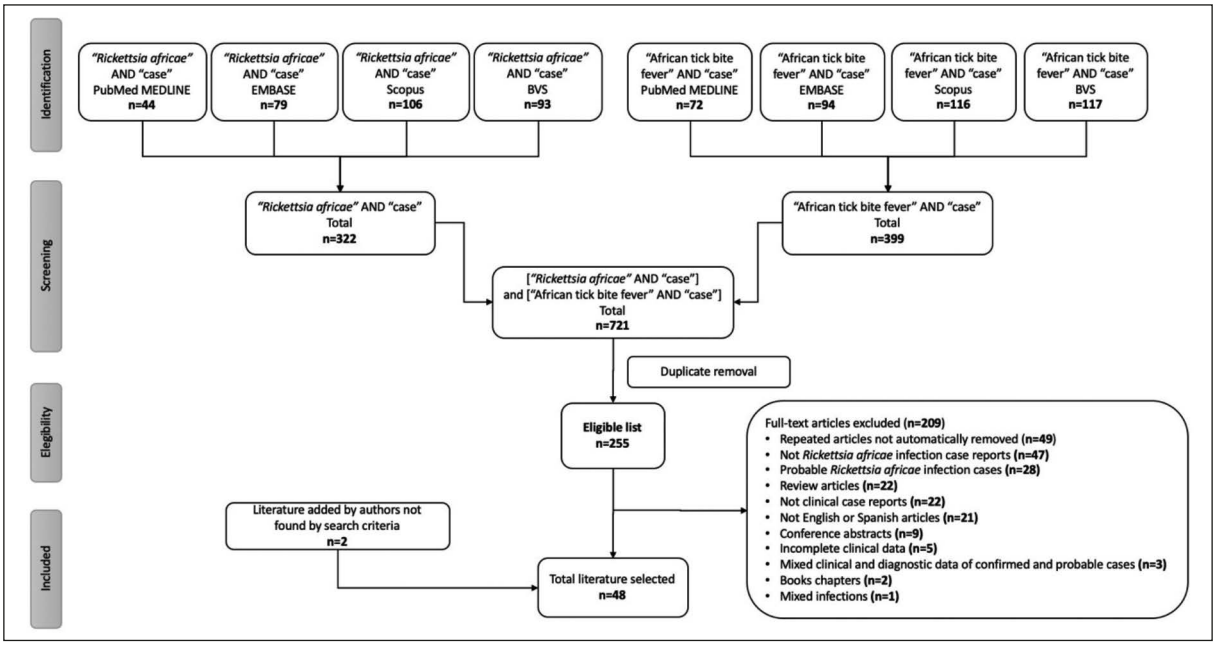

Figure 1 - Search strategy for the systematic review.

Table 1 - Demographic and epidemiological features of confirmed cases of *Rickettsia africae* infection

	Total cases n=108
*Age**	
0 – 17	2/100 (2%)
18 – 64	83/100 (83%)
≥ 65	15/100 (15%)
Sex†	
Male	61/103 (59.2%)
Female	42/103 (40.8%)
Autochthonous cases	8/108 (7.4%)
Cameroon	7/8 (87.5%)
Zimbabwe	1/8 (12.5%)
Imported cases	100/108 (92.6%)
Country of origin	
France	41/100 (41%)
Italy	11/100 (11%)
Norway	8/100 (8%)
United States	8/100 (8%)
Switzerland	5/100 (5%)
Netherlands	4/100 (4%)
Spain	4/100 (4%)
Germany	3/100 (3%)
Argentina	2/100 (2%)
Poland	2/100 (2%)
Portugal	2/100 (2%)
Sweden	2/100 (2%)
Australia	1/100 (1%)
Austria	1/100 (1%)
Brazil	1/100 (1%)
Israel	1/100 (1%)
Japan	1/100 (1%)
South Korea	1/100 (1%)
Slovenia	1/100 (1%)
Taiwan	1/100 (1%)
Country of travel[a]	
South Africa	74/97 (76.3%)
Swaziland	9/97 (9.3%)
Zimbabwe	8/97 (8.3%)
Tanzania	2/97 (2.1%)
Ethiopia	1/97 (1%)
Kenya	1/97 (1%)
Uganda	1/97 (1%)
Guadeloupe	1/97 (1%)
Cluster infection	
Yes	43/108 (39.8%)
No	65/108 (60.2%)
Tick exposure[b]	
Yes	43/71 (60.6%)
No	28/71 (39.4%)

*8 cases [36, 39, 59] were excluded due to missing data.
†5 cases [39] were excluded due to missing data.
[a]3 patients [27, 28, 33] were excluded due to traveling to more than one country.
[b]37 cases [13-15, 22-25, 27, 28, 30-34, 37, 39, 40, 43-45, 47, 51-53, 57, 58] were excluded due to missing data.

to age, sex, autochthonous cases, imported cases detailing country of origin and country of travel, history of cluster infection and tick exposure are shown in Table 1. Of all the reported cases, excluding missing information ("no data") of some variables, 2% were between 0-17 years, 83% were between 18-64 years, and 15% were 65 years of age or older. Regarding sex, 59.2% were men, and 40.8% were women. Of all reported cases only 7.4% were autochthonous and 92.6% were imported. Origin of autochthonous cases occurred in Cameroon in 87.5% and Zimbabwe in 12.5%. The origin of imported cases was mostly from France (41%), Italy (11%), Norway (8%), United States (8%), Switzerland (5%), Netherlands and Spain (4%); a few imported cases have also been reported in other countries such as Germany (3%), Argentina, Poland, Portugal and Sweden (2%), and Australia, Austria, Brazil, Israel, Japan, South Korea, Slovenia and Taiwan (1%) (Figure 2).

Probable country of infection, where travel was reported, mainly corresponded to South Africa (76.3%), Swaziland (9.3%) and Zimbabwe (8.3%); a few cases reported travelling to Tanzania (2.1%), Ethiopia, Kenya Uganda and Guadeloupe (1%) (Figure 3). Infection in clusters was reported in 39.8% of cases, and 60.6% reported history of tick exposure.

Clinical data

We analyzed fever, eschar, regional lymphadenopathy, lymphangitis, rash, and other clinical findings (Table 2). From all the reported cases, 89.8% had fever, 86.1% presented with an eschar, being a single eschar in 45.2% and multiple eschars in 54.8%. Enlarged regional lymph nodes were found in 50.9%, 11.1% had lymphangitis, and 41.7% developed cutaneous rash; 61.4% were papular, 56.8% macular, 47.7% vesicular, and only few cases were pustular (6.8%) or purpuric (4.6%) [15, 29-48].

Other clinical findings included headache (60.2%), myalgia (49.1%), chills (17.6%), arthralgia (9.3%), fatigue (9.3%) and malaise (6.5%). Five or fewer patients had cough, sore throat, odynophagia, nausea, back pain, local edema, aphthous stomatitis, diarrhea, abdominal pain, asthenia, hepatomegaly, sweating, neck pain, somnolence, anorexia, or conjunctivitis [15, 22, 23, 28, 29, 33, 35, 45, 51, 53, 58].

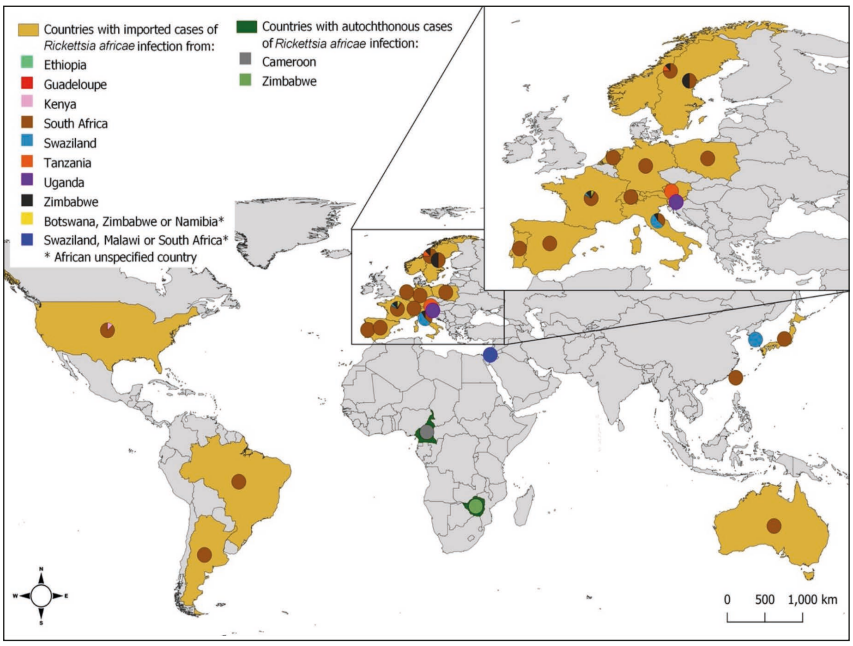

Figure 2 - Countries with imported and autochthonous cases of *Rickettsia africae* infection.

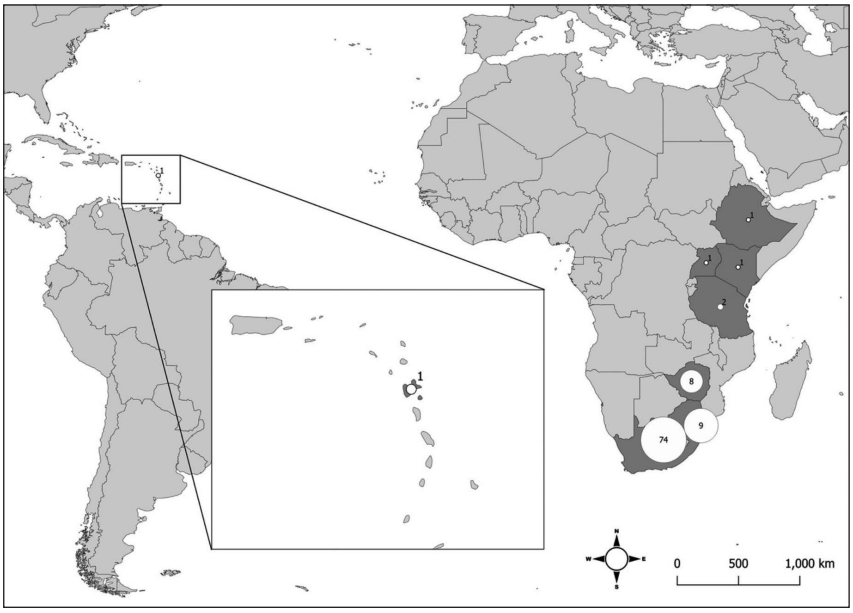

Figure 3 - Countries of travel related to imported cases of *Rickettsia africae* infection.

Laboratory manifestations

We analyzed hematologic and biochemical laboratory data (Table 3). From all reported cases, excluding missing information of some variables ("no data"), 70.7% presented with abnormal laboratory findings, of which 47.2% had elevated aspartate aminotransferase (AST), 47.2% elevated C-reactive protein (CRP), 41.5% elevated alanine aminotransferase (ALT), 32.1% leukopenia, 20.8% thrombocytopenia, and 15.1% elevated lactate dehydrogenase or gamma-glutamyl transferase. Five or fewer patients had other altered laboratory parameters such as increased erythrocyte sedimentation rate, alkaline phosphatase, creati-

Table 2 - Clinical features of confirmed cases of *Rickettsia africae* infection

	Total cases n=108
Fever	97/108 (89.8%)
Eschar	93/108 (86.1%)
Single	42/93 (45.2%)
Multiple	51/93 (54.8%)
Regional lymphadenopathy	55/108 (50.9%)
Lymphangitis	12/108 (11.1%)
Rash†	45/108 (41.7%)
Papular	27/44 (61.4%)[a]
Macular	25/44 (56.8%)[a]
Vesicular	21/44 (47.7%)[a]
Other	
Headache	65/108 (60.2%)
Myalgia	53/108 (49.1%)
Chills	19/108 (17.6%)
Arthralgia	10/108 (9.3%)
Fatigue	10/108 (9.3%)
Malaise	7/108 (6.5%)

†Some cases presented a mixed type of rash.
[a]1 case [13] was excluded due to missing data.

Table 3 - Laboratory findings of confirmed cases of *Rickettsia africae* infection

Laboratory findings	*Total cases n=108*
Abnormal laboratory findings*	53/75 (70.7%)
↑AST	25/53 (47.2%)
↑CRP	25/53 (47.2%)
↑ALT	22/53 (41.5%)
↓WBC	17/53 (32.1%)
↓PLT	11/53 (20.8%)
↑LDH	8/53 (15.1%)
↑GGT	8/53 (15.1%)
No alterations	22/75 (29.3%)

* 33 cases [4, 13, 15, 19-23, 26, 30, 31, 34, 37, 38, 43, 46, 54] were excluded due to missing data.
AST aspartate aminotransferase; CRP C-reactive protein; ALT alanine aminotransferase; WBC white-blood cells; PLT Platelets; LDH Lactate dehydrogenase; GGT gamma-glutamyl transferase.

nine, antiphospholipid antibodies, ferritin, total bilirubin, lymphopenia, leukocytosis, and monocytosis [15, 17, 19, 22, 25, 28, 29, 45, 52, 56]. Two cases (3.8%) were described as having "increased hepatic enzymes" not otherwise specified [39].

Treatment and outcomes

We analyzed antibiotic therapy, complications, need for hospitalization, and clinical outcomes (Table 4). From all reported cases, excluding missing information of some variables ("no data"),

Table 4 - Treatment, complications and outcomes of confirmed cases of *Rickettsia africae* infection

	Total cases n=108
*Antibiotic therapy**	
Monotherapy	83/90 (92.2%)
Doxycycline	77/83 (92.8%)
Ciprofloxacin	2/83 (2.4%)
Minocycline	1/83 (1.2%)
Amoxicillin	1/83 (1.2%)
Pristinamycin	1/83 (1.2%)
Rifampicin	1/83 (1.2%)
Combined therapy	7/90 (7.8%)
Doxycycline + Ciprofloxacin	2/7 (28.6%)
Doxycycline + Amoxicillin	1/7 (14.3%)
Doxycycline + Amoxicillin + Gentamicin	1/7 (14.3%)
Doxycycline + Amoxicillin + Oxacillin	1/7 (14.3%)
Minocycline + Ciprofloxacin	1/7 (14.3%)
Cotrimoxazol + Erythromycin	1/7 (14.3%)
Complications	4/108 (3.7%)
Purpuric cellulitis	2/108 (1.9%)
Myocarditis	1/108 (0.9%)
Neurological syndrome	1/108 (0.9%)
Need for hospitalization†	
Yes	9/72 (12.5%)
No	63/72 (87.5%)
Clinical outcome†	
Recovery	72/72 (100%)

*18 cases [13, 16, 22, 24, 26] were excluded due to missing data.
†36 cases [4, 13, 16, 22, 24, 26, 43, 51] were excluded due to missing data.

most of patients received antibiotic monotherapy (92.2%), and the remaining 7.8% received more than one antibiotic. From patients who received monotherapy, doxycycline was administered in 92.8%, ciprofloxacin in 2.4%, and minocycline, amoxicillin, pristinamycin or rifampicin in 1.2%. In all patients but one who received combined antibiotic therapy, at least one tetracycline antimicrobial (doxycycline or minocycline) was included. Complications occurred in 3.7% of cases, including purpuric cellulitis (1.9%), myocarditis (0.9%) and neurological syndrome (0.9%). Hospitalization was required in only 12.5%, and all cases had complete clinical recovery.

DISCUSSION

Demographic and epidemiological data

Our results show that *R. africae* infection, ATBF, is more frequent in the age group of 18-64 years

and has slightly greater incidence in males. This demographic pattern has also been described for other rickettsioses including Mediterranean spotted fever in Spain, scrub typhus in Australia [60, 61], *Rickettsia rickettsii* rickettsiosis in Brazil and *Rickettsia parkeri* rickettsiosis [62, 63]. Comparing our results with published cohorts or case series of SFG rickettsiosis in travelers and ATBF, similar results have been reported regarding sex and age [10, 11, 63, 64]. In our systematic review, although differences in sex frequency of infection is not high, predominance for males can be explained due to higher risk outdoor activities, which can favor the direct or indirect contact with tick bites (e.g., hunting, hiking, forestry, safari, among others) that are usually more often engaged in by males [65]. On the other hand, although travel has become an activity for all ages, youth and adults are the ones who travel the most, and ATBF is the most important rickettsial disease in travel medicine; thus, these two aspects could explain our results regarding age group related to *R. africae* infection [66, 67].

Considering the geographic origin of cases, we found that autochthonous cases represent less than 10% of all reported confirmed infections. Despite the facts that sub-Saharan Africa is endemic for ATBF and *R. africae* is widely distributed in Africa [68], autochthonous symptomatic cases seem to be rarely reported, probably because of many factors such as the mild clinical course of the disease, the infection in African people at an early age (developing an anamnestic antibody response), failure to detect classical signs including inoculation eschars that are not easily recognized in darkly pigmented persons, and the fact that definitive diagnosis is not established and reported, as it requires non-conventional molecular and serological tests (e.g., PCR or cross-absorption with WB) that are usually unavailable [68-70].

Data of epidemiological studies on ATBF in African communities are scarce. In 1991 Kelly et al. estimated an annual case incidence rates of ATBF as 60-80 per 10,000 patients in Zimbabwe, and subsequent serological studies in Central Africa (Cameroon) have been reported antibodies reactive with *R. africae* between 12-52%, and 32% among acutely febrile patients [70-72]. Interestingly, a recent study which assessed the knowledge, attitudes and practices on ATBF of rural livestock communities in the Eastern Cape Province of South Africa, showed that despite participants had frequent exposure to tick bites, they were not aware of *R. africae* infection nor that ticks are vectors of the disease [73], raising concerns about the potential risks posed by ATBF in the rural populace.

On the other hand, the mentioned literature has stated that ATBF is a frequent rickettsial acute undifferentiated febrile illness in travelers, and our results confirm this, as we found more than 90% of all reported cases occurred in travelers [67, 74-76]. European travelers represented more than the 80% of all imported infections, with France the country where most cases have been diagnosed, and South Africa the country where most *R. africae* infections were acquired. Thus, our results are in line with the multicenter GeoSentinel analysis of rickettsial diseases in international travelers, 1996-2008, which pointed out that Europeans have the highest frequency of infection, probably due to greater predilection to travel to underdeveloped countries for outdoor activities, and because more than 80% of SFG rickettsiosis has occurred in travelers in sub-Saharan Africa [67].

Interestingly, persons from the U.S. returning from Africa with a SFG rickettsiosis have been travelled to many countries including Congo, Gabon, Gambia, Liberia, Togo, Mozambique, Zambia, Botswana, Zimbabwe, Swaziland, Tanzania, Uganda, Kenya, Ethiopia and South Africa, and our results revealed confirmed *R. africae* cases in the last seven countries cited above [10]. Overall, the increasing tourism in rural areas such as Kruger National Park in South Africa, with outdoor activities, contribute to the high risk of exposure to vector-borne diseases [77].

Outbreaks of ATBF have been reported in groups of travelers, resulting in clusters cases, one of the most important epidemiological characteristics of *R. africae* infection [16, 78]. Group activities in endemic areas such as hunting, hiking, safari and other outdoor tourist activities represents an important risk factor for the development of infection in clusters [8, 11, 19]. Our results show that almost 40% of all reported cases occurred in clusters. Even though cluster infection frequency was not as high as other epidemiological aspects, it seems to be characteristic of ATBF and an important criterion for epidemiological diagnosis, since it is not a common feature in other SFG rickettsioses, with only few reported clustered cases in *R. rickettsii* and *Rickettsia japonica* infections [79-82].

In our analysis, tick exposure (tick-bite or seeing tick) was reported in 60% of cases, which is close to the percentage described for SFG rickettsioses in U.S. travelers returning from Africa (55%) [10], but not as high as other rickettsioses such as *R. rickettsii* in Brazil (72%) and *R. parkeri* rickettsiosis (92%) [63, 83]. Tick vectors, *A. hebraeum* and *A. variegatum*, are reservoirs of *R. africae* as they transmit the infection to their offspring by transovarial transmission; thus, not only the adult stage is involved in tick-bite transmission, and also larvae and nymphs, which are smaller, not easy to see and be recognized by people, explaining why many patients do not report history of tick exposure during travel [84, 85].
Curiously, a recent study described the first detection of an *A. variegatum* infesting a sheep on the island of Sardinia, Italia, and the detection of *R. africae* in this tick [86, 87]. The authors pointed the above as an occasional finding, probably linked to the migrating birds from Africa during summer [87]. In fact, previous Italian studies had reported *R. africae* in *Ixodes ricinus*, and in endemic ticks of African continent, like *Amblyomma* and *Hyalomma*, removed from migratory birds, as well, raising the needed to better investigate the role of these animals in the epidemiology of ATBF in non-endemic areas [86, 88].

Clinical data
Clinically, *R. africae* infection presents classical features of tick-borne rickettsiosis, such as fever, eschar at the tick-bite site, rash and nonspecific symptoms including headache, myalgia, regional lymphadenopathy, among others [89, 90]; however, previously published cohorts or case series of ATBF have emphasized eschar as usually multiple, regional lymphadenopathy present even in the absence of the eschar, presence of lymphangitis, and cutaneous rash usually being absent or developed only close to the inoculation site [11, 64]. In our review, more than 80% of the cases had fever and inoculation eschar, rash was not a common sign as it was present in less than 50% of cases, and frequent nonspecific symptoms were headache and myalgia. Considering single or multiple eschars, our results revealed that more than 50% of cases developed multiple eschars, which is in line with previous publications [8, 11]. Multiple eschars develop due to the aggressive behavior of *A. variegatum* and *A. hebraeum*, high portion of which carry *R. africae*, thus people are often bitten by multiple infected ticks simultaneously [8, 85, 91, 92]. Multiple eschars seem to be a characteristic of ATBF; this clinical finding has described in other rickettsioses such as infections caused by *R. conorii* or *Orientia tsutsugamushi* [93, 94].
Comparing our results with other studies on confirmed and probable cases of ATBF and SFG rickettsioses in U.S. travelers returning from Africa, our data was more similar to the reported of Raoult et al. regarding fever (88%), inoculation eschar (95%) (single [46%] or multiple [54%]) and rash (46%) [10, 11, 64]. In addition, it is worth mentioning that our results identified lymphangitis as a clinical finding in 11% of *R. africae* infections, highlighting, as other authors, that it is not a specific feature of infection caused by *Rickettsia sibirica* subsp. *mongolitimonae* [12].

Laboratory features
Regarding laboratory features, rickettsial diseases, whether as mild or severe illness, present common abnormalities such as mild leukopenia, increased C-reactive protein, thrombocytopenia, and moderately elevated transaminases [95, 96]. Our results show that at least 70% of ATBF cases had at least one abnormal laboratory parameter. Increases in transaminases, C-reactive protein and leukopenia were the main features described in *R. africae* infection, which are common in rickettsioses [95, 96]; however, none of them is specific for this rickettsiosis. Unfortunately, we were unable to analyze levels of these laboratory parameters.

Treatment, complications and outcomes
Regarding antibiotic therapy, tetracycline-class antibiotics (doxycycline and minocycline) were used in more than 90% and 80% of patients which received monotherapy and bitherapy, respectively, which is in line with this antibiotics-class as the therapy of choice for rickettsioses [97]. Thus, it is probable that in cases treated with betalactams (ineffective against rickettsiae) and a tetracycline was effective treatment for the rickettsial infection. Only one patient of bitherapy did not receive a tetracycline-class antibiotic. Other antibiotics that are effective in the analyzed cases were ciprofloxacin, pristinamycin, and rifampicin [97, 98]. One patient was treated with a β-lactam-group antibiotic (amoxicillin), which is ineffective for treatment of rickettsiosis; nevertheless, this

patient did not require hospitalization and had a full clinical recovery [15, 97].
Complications *in R. africae* infection are rare, and we found them in less than 5% of confirmed cases. They included purpuric cellulitis, neurological syndrome and myocarditis. Other complications reported in the scientific literature, considering probable ATFB cases, included convalescent-phase asthenia, reactive arthritis and peripheral neuropathy [65, 99].
Fatal outcomes have never been reported for ATBF. Moreover, according to our results, hospitalization was reported in less than 15% of cases, and compared with severe rickettsiosis such as *R. rickettsii* and *R. conorii* infections [87, 100], ATBF has a mild clinical course and a favorable prognosis [8].

CONCLUSIONS

This systematic review provides a thorough evaluation of clinical, epidemiological, and laboratory features of *R. africae* infection, ATBF. The disease presents as a mild febrile illness, associated with multiple eschars in half of the cases, with a tick exposure not always recognized and occurring in cluster in a third of cases. Increased transaminases, C-reactive protein and leukopenia are the main laboratory features. The disease is not fatal, but complications can occur. Travelers to endemic regions for outdoor activities in sub-Saharan Africa are at risk of acquiring *R. africae* infection. As far as the molecular diagnostic methods are available to identify the *Rickettsia* species, it must be important a routinely microorganism detection in ticks that bite humans, and in clinical samples from people with history of tick-bites.

Authors' contributions
CRSR and ÁAFM designed the study and searched the literature. CRSR did the systematic review and wrote the draft manuscript. CRSR and ÁAFM did the data analysis, data interpretation, critically reviewed the methods and results, and wrote the original manuscript. CRSR and ÁAFM have verified the underlying data. CRSR and ÁAFM have accessed to verified the underlying data.

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Conflicts of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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