Unraveling the epidemiological relationship between ticks and rickettsial infection in Africa

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Tick-borne rickettsioses are emerging and re-emerging diseases of public
health concern caused by over 30 species of *Rickettsia*. Ticks are obligate
hematophagous arthropods with over 700 species of Ixodid ticks known
worldwide. The escalating geographical dispersal of tick vectors and
concomitant increase in the incidences of tick-borne diseases have fueled
interest in the ecology of tick-borne pathogens. This review focuses on aspects
of the *Rickettsia* pathogen, including biology, taxonomy, phylogeny, genetic
diversity, epidemiology of the disease, and the role of vertebrate host in the
perpetuation of rickettsioses in Africa. Our review also highlights some of the
species of *Rickettsia* that are responsible for disease, the role of tick vectors
(both hard and soft ticks) and the species of *Rickettsia* associated with diverse
tick species across the continent. Additionally, this article emphasizes the
evolutionary perspective of rickettsiae perpetuation and the possible role of
amplifying vertebrate host and other small mammals, domestic animals and
wildlife in the epidemiology of *Rickettsia* species. We also specifically,
discussed the role of avian population in the epidemiology of SFG rickettsiae.
Furthermore, we highlighted tick-borne rickettsioses among travelers due to
African tick-bite fever (ATBF) and the challenges to surveillance of rickettsial
infection, and research on rickettsiology in Africa. Our review canvasses the
need for more rickettsiologists of African origin based within the continent to
further research towards understanding the biology, characterization, and
species distribution, including the competent tick vectors involved in their
transmission of rickettsiae across the continent in collaboration with
established researchers in western countries. We further highlighted the
need for proper funding to encourage research despite competing demands
for resources across the various sectors. We finalize by discussing the
similarities between rickettsial diseases around the world and which steps
need to be taken to help foster our understanding on the eco-epidemiology
of rickettsioses by bridging the gap between the growing epidemiological data
and the molecular characterization of *Rickettsia* species.

KEYWORDS

spotted fever, *rickettsia* spp., ticks, Africa, epidemiology

Introduction

Vector-borne diseases (VBDs) comprise an expanded group of diseases that are caused by a collection of pathogens transmitted by arthropod vectors, such as fleas, mosquitoes, ticks, and sand flies (1). In recent decades, vector-borne zoonotic pathogens have gained increasing attentions globally, with several reports of emerging and/or re-emerging pathogens registered in both vertebrate and invertebrate hosts. Some vector-borne bacterial pathogens are responsible for acute febrile illnesses, with potentially fatal or severe outcomes. Vector-borne rickettsiosis (VBR) is a disease caused by a group of gram-negative bacteria transmitted by lice, mites, fleas, and ticks (2). The genus *Rickettsia* (Rickettsiales: Rickettsiaceae) comprises obligate intracellular Alphaproteobacteria responsible for diseases that affect diverse eukaryotic hosts (3). Rickettsial species differ considerably with respect to their association with arthropods, pathophysiology, behavior of the vector to infection, and disease outcome (4). In the tropical and subtropical regions of the world, VBD is most often prevalent and affects poor communities with the least access to healthcare, with significant health threats to the inhabitants of these areas. The life cycle of VBR is complex, involving hematophagous arthropod vectors and vertebrate hosts, with the former also serving as the main reservoirs. The majority of emerging VBR are tick-borne and are caused by rickettsial species belonging to the spotted fever group (SFG) (5).

Ticks are hematophagous arthropods, second only to mosquitoes, which are the leading vectors of human pathogens (6). It is worth noting that ticks from all regions are carriers of specific pathogens that may be unknown to healthcare providers in other parts of the world. Numerous tick species of the genera *Hyalomma* (*Hy*), *Amblyomma* (*Am*), *Rhipicephalus* (*Rh*), *Ixodes* (*I*), *Haemaphysalis* (*Hae*), and *Dermacentor* (*D*) have been implicated as vectors of rickettsial pathogens (7–9). Hard ticks (Acari: Ixodidae) are considered the most important arthropod group that harbors rickettsial organisms (10). At least 27 of the more than 30 published rickettsial species are intricately linked with hard ticks (11). Approximately 17 of these species have been isolated or detected in African arthropods (12, 13). Rickettsiae associated with ticks are usually transmitted vertically (transovarial transmission) from engorged females to their offspring. This phenomenon is speculated to be the single most important mechanism driving permanent perpetuation of rickettsiae among tick populations (14). Conversely, some species of *Rickettsia* can deleteriously affect tick population size by decreasing female reproductive performance (15–17). Long-term perpetuation of rickettsial species largely depends on the availability of amplifying vertebrate hosts, which serve as infection sources (horizontal transmission), thereby creating new cohorts of *Rickettsia*-infected ticks (18, 19). Ticks can spread into any territory that provides favorable conditions for their survival; under optimal temperature and relative humidity, ticks can reproduce and spread their bacterial pathogens.

Tick-borne rickettsioses (TBRs) are distributed worldwide and are considered among the most frequently identified etiologies of systemic febrile illness, after malaria, among international travelers. Therefore, they play an important role in public health (20, 21). The epidemiology of any type of rickettsial disease transmitted by ticks mirrors the ecological distribution and seasonal activity of implicating tick vectors and their hosts involved in the transmission of these pathogens. Additionally, human behaviors that expose people to tick attachment and subsequent infections also play a role (22). Each tick species has a particular set of optimal environmental conditions and biotopes that ultimately influences the geographical distribution of the ticks; therefore, the type of TBR, as only a handful of tick species, is distributed globally.

Rickettsioses are emerging and re-emerging VBD of global importance (11). Several SFG *Rickettsia* species associated with human and animal diseases have been reported worldwide (23). These species include *Rickettsia africae* [the etiological agent of African tick bite fever (ATBF)], *Rickettsia conorii* [Mediterranean spotted fever (MSF)], *Rickettsia aeschlimannii* (innominate rickettsioses), and *Rickettsia sibirica* (lymphangitis-associated rickettsioses) (24). There are also non-pathogenic endosymbiont species in *Rickettsia*. SFG rickettsial pathogens are transovarially transmitted depending on vertebrate hosts as pathogen reservoirs (24). Thus, ticks are regarded not only as efficient vectors but also as competent reservoirs. Clinical signs may include fever and rash that may be maculopapular, vesicular, or purpuric in severe cases, and may be absent, as seen in Rocky Mountain spotted fever (RMSF) (6). These rickettsial diseases can be mild, severe, or even fatal. One of the hallmarks of most SFG rickettsioses is the typical inoculation eschar at the site of tick bite (25).

In the last decades, some species of *Rickettsia* that were otherwise thought to be not prevalent and distributed in Africa have been reported by detection of their genetic material using molecular based diagnostics including sequencing. Also, rickettsioses are seldom considered when patients with undifferentiated febrile illness are evaluated, and due to the overlapping symptoms with other illness endemic in parts of Africa such as malaria, yellow and dengue fevers, clinical diagnosis is difficult in the absence of confirmatory laboratory tests. Therefore, it is expedient that this information is brought to the front-burner to enlighten healthcare providers and government on this emerging but neglected disease. Also, they lack adequate surveillance of ticks, livestock, wildlife, and companion animals for tick-borne zoonotic pathogens, specifically *Rickettsia* species. Aside from the Mediterranean region comprising North Africa, most of the sub-Saharan African (SSA) nations do not have dedicated research centers or institutes for research on *Rickettsia*. Many studies conducted in most African countries are based on scientific collaboration

involving ferrying of samples to developed western nations for molecular characterization and confirmation. Due to underfunding and/or paucity of well-trained manpower, surveillance is lagging compared to other continents of the world. We hope the scientific content of this review will further bring attention to the urgent need of budgetary allocations to fund research and clinical diagnostics to better improve our scientific understanding and healthcare associated with these important diseases. In a nutshell, this review aims to gather, summarize, and present an updated knowledge about epidemiological aspects of members of the genus *Rickettsia* with particular emphasis on the SFG in Africa.

Methods

We performed a deep bibliographic search of the CABS Abstracts database (accessed 29th November 2021). Keywords used for the search were "*Rickettsia*," "Ticks," and "Africa". These keywords were mapped to the subjects' headings. In addition, we used the Boolean operator "AND" in combination with these words as the major focus in our review, which focused on the epidemiology and relationship between ticks and rickettsial infection, with emphasis on SFG rickettsiae in Africa. The search yielded 216 references. The list of papers was checked manually by screening the title and abstract of each reference as part of preliminary filtering. Papers that did not directly address the topic were excluded. All relevant papers were downloaded and subjected to full-text evaluation, and the relevant text was extracted from each paper and used for preparing this review. Text word searches were performed on multiple additional terms that were tailored to specific questions. We also checked the reference lists of the included articles and searched for additional relevant citations. In some instances, textbook references were used to support statements considered as known knowledge in the field. The selected articles were in English only. The 200 papers used in this review were cut across several article types, including original research, short communication, letters to the editor, review(s), and opinion papers. The earliest article was published in 1910, whereas the most recent article was published in 2022. The geographical origins of the bulk of the papers covering the epidemiological aspects of the review were prevalence studies, principally conducted across all regions of Africa. Additionally, we observed that most of the laboratory research work might have been carried out in laboratories in developed countries after field surveys in Africa. Therefore, the authorship of published papers cut across both Africans and experts in Western nations. Some topics covered in our review, but not exclusive to the published papers used in writing this review on spotted fever group rickettsiae and associated tick vectors, include genetics, epidemiology, diagnostics, vectorial capacity, and clinical and travel medicine.

Rickettsiae properties, taxonomy, phylogeny, and genotyping

With sizes ranging from 0.3–2.0 μm, rickettsiae are strictly intracellular bacteria and they multiply inside the cytoplasm of eukaryotic host cells by binary fission (26). The genus *Rickettsia* can be divided into four different phylogenetic groups: (i) the spotted fever group (SFG), with over 20 known species, all closely associated with ticks; species of *Rickettsia* belonging to this group affect human health. Examples within the SFG include *R. conorii, Rickettsia rickettsii, R. africae, R. sibirica*, and *Rickettsia parkeri*. (ii) Typhus group (TG), containing two species, *Rickettsia typhi* and *Rickettsia prowazekii*, which are transmitted by fleas and louses and cause diseases that affect human health. (iii) The transitional group (TRG) contains rickettsial pathogens responsible for human disease and is primarily associated with diverse arthropods, including ticks (*Rickettsia australis*), fleas (*Rickettsia felis*), and mites (*Rickettsia akari*). (iv) The ancestral group (AG), represented by two tick-associated organisms, namely *Rickettsia bellii* and *Rickettsia canadensis* (3, 11, 27).

To date, the genus *Rickettsia* comprises over 30 formally recognized species, among other uncharacterized strains. Taxonomic guidelines for species identification and description of new isolates have been proposed, utilizing sequences of the 16S rRNA (*rrs*) gene and four protein-coding genes: *glt*A, *omp*A, *omp*B, and gene D (28). Rickettsiae phylogeny has enabled precise identification and classification of rickettsiae. Based on 16S rRNA (*rrs*) gene sequences, the genus *Rickettsia* belongs to group 1 of a subclass of Proteobacteria (29). High levels of conservation in the 16S rRNA gene sequences among members of the genus *Rickettsia* constitute a setback for significant inferences about intragenus phylogeny (30). The genes encoding outer membrane proteins, surface cell antigens (*omp*A, *omp*B, *sca*1, *sca*2, and *sca*4), and citrate synthase (*glt*A) have been regarded as sufficiently variable to infer dependable phylogenetic relationships among rickettsiae (31–34). Furthermore, the availability of complete genome sequences has enabled phylogenomic approaches, which have provided clarity to some extent regarding the phylogenetic relationships among rickettsiae (35, 36). Large amounts of data have been generated owing to genomic sequencing, and these data are useful for evaluating the reliability of recognized groups. Furthermore, by sequencing rickettsial species, phylogenetic studies should be reinforced.

Rickettsial infection in Africa

Several *Rickettsia* species amplified in ticks collected from livestock and domestic animals across different geographical regions of Africa are summarized in Table 1. Many *Rickettsia*

TABLE 1 Overview of Spotted Fever Group *Rickettsia* detected in ticks collected from livestock and domestic animals across Africa.

Country	Host animal	Tick species	SFG rickettsiae	Reference
Sao Tome and Principe	Cattle, goats	Amblyomma astrion	Rickettsia africae	(37)
Ethiopia	Cattle	Amblyomma cohaerens	Rickettsia africae	(38)
Liberia, Republic of Congo	Cattle	Amblyomma compressum	Rickettsia africae	(39, 40)
Ethiopia, Uganda, Kenya	Cattle, dromedaries	Amblyomma gemma	Rickettsia africae	(41–44)
South Africa	Cattle, goats, dog	Amblyomma hebraeum	Rickettsia africae	(45–47)
Djibouti, Kenya	Cattle	Amblyomma lepidum	Rickettsia africae	(43, 48)
Kenya	Cattle, sheep, goats	Amblyomma sparsum	Rickettsia africae	(42)
Benin, Mali, Ivory coast, Liberia, Guinea, Nigeria, Senegal, Burkina Faso, Angola, South Africa, Mozambique, Cameroon, Uganda, Djibouti, Kenya, Ethiopia, Sao Tome and Principe, Union of the Comoros, Sudan	Cattle, donkeys, sheep, goats	Amblyomma variegatum	Rickettsia africae; Rickettsia africae-like species (RAL); Rickettsia spp.	(37–39, 41, 42, 48–63)
Algeria	Pigs	Dermacentor marginatus	Rickettsia slovaca	(64)
Guinea	Dogs, goats	Haemaphysalis paraleachi	Rickettsia africae, Rickettsia massiliae	(40)
South Africa	Dogs	Haemaphysalis elliptica	Rickettsia africae	(45)
Nigeria, Uganda	Dogs	Haemaphysalis leachi	Rickettsia spp., Rickettsia conorii conorii, Rickettsia massiliae	(65, 66)
Algeria	Cattle	Hyalomma anatolicum excavatum	Rickettsia aeschlimannii	(64)
Algeria	Sheep	Hyalomma detritum detritum	Rickettsia aeschlimannii	(67)
Tunisia, Nigeria, Sudan, Algeria	Camel	Hyalomma dromedarii	Rickettsia aeschlimannii, Rickettsia africae	(25, 68–72)
Ivory Coast, Nigeria, Senegal, Ethiopia, Egypt	Cattle, camel	Hyalomma impeltatum	Rickettsia africae, Rickettsia aeschlimannii; Rickettsia africae-like species (RAL)	(41, 53, 54, 57, 68, 73, 74)
Ivory Coast	Cattle	Hyalomma impressum	Rickettsia spp.; Rickettsia africae	(52)
Ivory Coast, Algeria, Morocco	Cattle, sheep	Hyalomma marginatum marginatum	Rickettsia spp.; Rickettsia africae; Rickettsia aeschlimannii	(52, 67, 75)
Mali, Nigeria, Senegal, Guinea, Ethiopia, Burkina Faso, South Africa, Cameroon, Kenya, Niger, Egypt, Algeria, Zimbabawe, Sudan	Cattle, camel, donkeys, sheep, goats, horses	Hyalomma marginatum rufipes	Rickettsia spp., Rickettsia aeschlimannii; Rickettsia africae	(40–42, 50, 56, 57, 61, 68, 71, 73, 74, 76–80)
Algeria	Cattle	Hyalomma scupense	Rickettsia aeschlimannii	(64)
Mali, Ivory Coast, Senegal, Nigeria, Ethiopia, Cameroon, Kenya, Sudan, Egypt	Cattle, camel, donkeys, sheep, goats, horses, dromedaries	Hyalomma truncatum	Rickettsia spp. Rickettsia africae Rickettsia aeschlimannii; Rickettsia sibirica mongolitimonae	(41–43, 50, 52, 56, 68, 69, 73, 76)
Liberia	Dogs	Ixodes muniensis	Rickettsia raoultii Khabarovsk	(40)

(Continued)

TABLE 1   Continued

Country	Host animal	Tick species	SFG rickettsiae	Reference
Algeria	Cattle	Ixodes ricinus	Rickettsia helvetica, Rickettsia monacensis	(81)
Senegal, Guinea, Nigeria, Djibouti	Cattle	Rhipicephalus (Boophilus) annulatus	Rickettsia africae Rickettsia africae-like species (RAL) Rickettsia aeschlimannii	(40, 48, 53, 76)
South Africa, Union of Comoros	Donkey	Rhipicephalus (Boophilus) appendiculatus	R. aeschlimannii, Rickettsia africae	(51, 61)
Ivory Coast, Guinea, South Africa, Ethiopia	Cattle, sheep	Rhipicephalus (Boophilus) decoloratus	Rickettsia africae, Rickettsia spp.	(40, 54, 60, 82)
Ivory Coast, Liberia;	Cattle	Rhipicephalus (Boophilus) geigyi	Rickettsia africae	(40, 54)
Mali, Ivory Coast, Union of Comoros	Cattle	Rhipicephalus (Boophilus) microplus	Rickettsia spp.; Rickettsia africae	(51, 52, 54, 56)
Algeria	Cattle	Rhipicephalus bursa	Rickettsia massiliae	(64)
Mali, Senegal, Nigeria, South Africa, Uganda, Kenya, Ethiopia	Cattle, horses, sheep, donkeys, goats	Rhipicephalus evertsi evertsi	Rickettsia spp., Rickettsia africae, Rickettsia aeschlimannii; Rickettsia conorii spp. Rickettsia africae-like species (RAL)	(42, 53, 56–58, 60, 61, 76, 82)
Senegal	Donkeys, cattle	Rhipicephalus guihoni	Rickettsia massiliae	(76)
Kenya	Cattle, sheep, goats	Rhipicephalus pulchellus	Rickettsia aeschlimannii	(42)
Mali, Ivory Coast, Nigeria, South Africa, Tunisia, Algeria	Cattle, dogs, cats, goats, sheep	Rhipicephalus sanguineus (sensu lato)	Rickettsia spp.; Rickettsia aeschlimannii Rickettsia africae, Rickettsia conorii israelensis; Rickettsia raoultii, Rickettsia massiliae, Rickettsia monacensis, Rickettsia conorii subsp. conorii	(45, 54, 56, 57, 64, 65, 83–85)
Ivory Coast; Liberia	Cattle, goats, dogs	Rhipicephalus senegalensis	Rickettsia spp; Rickettsia massiliae	(40, 52)
South Africa	Donkey, dog	Rhipicephalus simus	Rickettsia spp.	(45, 61)
Ivory coast, South Africa	Dogs, sheep	Rhipicephalus spp.	Rickettsia massiliae; Rickettsia raoultii	(83, 86)
Ivory coast	Cattle	Rhipicephalus spp. (nymph)	Rickettsia africae	(54)
Nigeria, Tunisia	Dogs, sheep, goats	Rhipicephalus turanicus	Rickettsia spp., Rickettsia massiliae, Rickettsia monacensis	(65, 84)

species have been shown to cause acute infectious diseases in humans, as described below.

African tick-bite fever

Rickettsia africae is the etiological agent of ATBF and is transmitted *via* the bite of ticks belonging to the genus *Amblyomma* (specifically, *Am. hebraeum* and *Am. variegatum*) (87–89). These tick species are common among rural

communities in parts of SSA and pose a threat to local populations. In Zimbabwe, the annual incidence rate of ATBF is estimated to be approximately 60–80 cases per 100,000, where the tick vector is endemic (9). Nonetheless, the most documented cases are among travelers from Europe, while reports from native populations are scarce. The ATBF was discovered by Pijper in 1930 (90). However, the isolate was lost, but it was subsequently isolated from humans in 1990; by 1996, it was named *R. africae* (87). This condition presents as a sudden onset of fever (59–100%), nausea, headache (62–83%),

and neck myalgia (81%), and begins 5–10 days after tick bite (9, 91). Inoculation eschar (53–100%) develops in most patients at the spot of a tick bite, which is predominantly localized in the lower limbs and accompanied by regional lymphadenopathy (inguinal) (92). Multiple eschars can be observed in approximately 54% of the affected patients (9). Further, a generalized maculocutaneous rash (15–46%) has been observed close to the eschar. Neurological involvement, including encephalopathy and neuropathy, has also been reported (91). Other clinical manifestations include painful sacral syndrome, retinitis, and pan-uveitis (93, 94). Humans are considered accidental hosts, and no known fatal cases have been recorded (95). In febrile patients (travelers) returning from the tropics, ATBF should be considered along with malaria as a differential diagnosis. In SSA, ATBF has been reported with a high incidence in Senegal (21.4–51%) (76) and Cameroon (11.9–51.8%) (96). *Rickettsia africae* has been detected in ticks and, in some cases, in humans among travellers by PCR in several countries in Africa, including Chad, Sudan, Ethiopia, Niger, Mali, South Africa, and many other countries across the continent (76, 92). The prevalence of *R. africae* in ticks is > 50% in Uganda and Nigeria (49), Cameroon (50), the Union of the Comoros (51), and Cote d'Ivoire (52).

Mediterranean spotted fever

One of the oldest VBD is MSF, which is endemic to the Mediterranean area (comprising northern Africa and southern Europe), although sporadic cases have been reported in southern Africa and central Europe (9). MSF is the most common human tick-borne rickettsiosis in North Africa (97). MSF was caused by *R. conorii* subspecies *conorii* and was relatively unknown until 1909, when the first case was described in Tunisia (98). The first clinical case of MSF rickettsiosis was described by Conor and Brush in 1910 (98). The vector was unidentified until 1930 when, in Tunisia, crushed infected *Rh. sanguineus* ticks were inoculated into patients, and the patient contracted MSF (99). Patients with MSF, also referred as "boutonneuse" fever, typically have high fever (100%), influenza-like symptoms (chills, headache and arthromyalgias), generalized maculopapular rash (97%)— usually on the extremities and subsequently on the trunk involving the soles, palms, and to a lesser extent on the face. An eschar or "tache noire" (local necrotic inflammation characterized by a black crust) at the site of the tick bite may be observed in affected patients (8, 100). The eschar may not be found in some cases and is rarely observed at multiple sites (100). Other clinical features of MSF in affected patients include hepatomegaly (44%), splenomegaly (19%), and gastrointestinal symptoms (30%). The presence of either unilateral or bilateral conjunctivitis may represent an eye inoculation site for the bacterium (9). Brown dog ticks (*Rh. sanguineus*) is the main

vector and reservoir, and this pathogen has also been reported in other tick species such as *Rh. evertsi evertsi*, *Rh. muhsamae*, *Rh. simus*, *Hae. leachi*, and *Hae. punctaleachi* (7, 8, 101). Most cases of MSF occur in summer (between July and October), similar to reports from southern Europe (8, 97). This period coincided with warm climatic conditions that were favorable to the vector, with increased aggressiveness, propensity, and expansion of *Rh. sanguineus* (102). The major risk factor for MSF is direct contact with dogs and domestic animals (97, 103, 104). Due to the influence of climate change, it was hypothesized that the host-seeking and feeding behaviors of *Rh. sanguineus* tick vectors could have been altered by these climatic circumstances (97), as observed for other tick species (105, 106). MSF has been reported in Algeria (97), Morocco (103), and Tunisia (104). *Rickettsia conorii* subspecies *conorii* has also been detected in ticks in Chad, Kenya, Somalia, and South Africa (100).

Israeli spotted fever

Rickettsia conorii subspecies *israelensis*, the causative agent of Israeli spotted fever (ISF), belongs to the *R. conorii* complex, and was first isolated in Israel in 1974 by Goldwasser (107). This subspecies is genetically related to the etiological agent of MSF, *R. conorii* subsp. *conorii* (108). It is one of the most severe and life-threatening rickettsial infections worldwide. *Rhipicephalus sanguineus* is a vector and potential reservoir for *R. conorii* subsp. *israelensis* (8). This tick species has a low affinity for hosts other than dogs (109). Just like MSF, human cases of ISF are sporadic (110, 111). These cases have been described in Portugal and Italy (112). Clinical manifestations are similar to those of other SFG except for the absence of eschar (90%) at the site of tick bite, and when visible, it resembles a small, pinkish papule (4, 9). Additionally, a history of tick exposure is not always present (111, 112). Several forms and fatal cases of ISF have been documented, mostly among travelers and people with deficiency in glucose-6-phosphate dehydrogenase (9). In one of the cases reported in southern Tunisia, the patient had a history of previous travel to Libya (two weeks) and had worked in the livestock industry (113). Another confirmed reported case of ISF involved a Swiss tourist who took a seven-day cruise on the Mediterranean Sea and sailed along the coast of Libya, Malta, and Crete (109). During the trip, he visited a handful of archaeological sites in Libya, and unfortunately, he lost his life (109). As there is no documented case of ISF in other locations (Malta & Crete) visited by tourists, we can say that the geographical distribution of ISF extends to North Africa and Libya. The similarity in vector types for both ISF and MSF denotes evidence of geographical overlap between the two diseases. *R. conorii* subsp. *israelensis* has also been detected in blood DNA and ticks (*Rh. sanguineus*) in an epidemiological survey of tick-borne pathogens in dogs in Nigeria (65), and in *Rh. appendiculatus* ticks in Cameroon (50).

Rickettsia sibirica mongolitimonae infections

Rickettsia sibirica mongolitimonae was initially named HA-91 based on serotyping (114) and was first isolated from *Hy. asiaticum* ticks collected from Mongolia in 1991 (115). This organism is regarded as a subspecies of the *R. sibirica* group and exhibits ecological and serotypic specificity (116). This *Rickettsia* species causes lymphangitis-associated rickettsiosis (LAR) due to lymphangitis and lymphadenopathy that occur with this infection (4). The clinical features of the reviewed cases included headache (100%), myalgia (100%), fever, chills (19%), eschar on the upper or lower limbs, enlarged lymph nodes, lymphangitis (46.1%), and generalized maculopapular rash, particularly on the palms and soles (116, 117). Recently, a patient returning from Cameroon with a confirmed case of rickettsiosis due to *R. sibirica mongolitimonae* did not show any signs of lymphadenopathy or lymphangitis (118). Lymphangitis has also been described in ATBF, although it is less pronounced (95). In general, *R. sibirica mongolitimonae* infection is mild, with complications such as disseminated intravascular coagulation, shock, acute renal failure, neurological disorders, retinal vasculitis, and atrial fibrillation (118). The clinical features presented herein may prove to be helpful, but they are not exhaustive for the diagnosis of LAR. Therefore, it is likely that their distribution is more widespread than geographically reported. LAR primarily occurs between March and September. Several cases have been confirmed in patients from different nationalities in Southern Europe, with the majority of cases recorded in patients from France (116). Therefore, *Rickettsia sibirica mongolotimonae* is endemic in southern France, Africa, and Asia (116). The competent tick vector for this pathogen in Southern Europe, including France, is currently unknown. Although *Hyalomma* ticks are extensively distributed in these areas, *Hy. asiaticum* has been implicated as a competent vector in China (Asia) (115) and Algeria (North Africa, a part of the Mediterranean) (119). In other parts of Africa—Mali and Senegal—*R. sibirica mongolitimonae* has been detected in *Hy. truncatum* (33, 76). Therefore, further studies including transmission experiments are needed to clarify the role of this tick vector as the possible vector in the Mediterranean region comprising southern France and other parts of northern Africa.

Four human cases have been documented in Algeria, Egypt, Cameroon, and South Africa (118, 120). Cases occur frequently during the spring season (116); however, the clinical spectrum and epidemiology of infection with *R. sibirica mongolitimonae* must be further analyzed to understand the disease. It has also been detected in ticks collected from the Niger Republic and Senegal (118). It appears that *Hyalomma* spp. ticks are associated with *R. sibirica mongolitimonae*, with DNA detected in *Hy. truncatum* in Mali and Senegal (33, 76) and *Hy. aegyptium* ticks in Algeria (119); however, transmission experiments are necessary to clarify the role of these ticks as vectors or reservoirs for this rickettsiae.

Innominate rickettsioses (*R. aeschlimannii* infection)

The infection is caused by *R. aeschlimannii*, which was first isolated in Morocco in 1992 from *Hy. marginatum* ticks (8, 75). Further, *R. aeschlimannii* has been detected in this tick species in North Africa and southern Europe (67). The first documented human infection was in a French patient who became ill after a trip to Morocco. The symptoms were similar to those of MSF, including high fever, eschar on the ankle, and generalized maculopapular rash (121). In Tunisia, *R. aeschlimannii* has been confirmed by serology in a human patient (122) as well as in two human subjects in Algeria using immunofluorescence (IF) and western blot (WB) assays (123). It has also been reported in humans from different locations in Africa, with the majority being in North Africa. For instance, it has been confirmed in a South African citizen returning from a hunting trip (124). In most published studies, *R. aeschlimannii* strains have been documented in ticks belonging to the genus *Hyalomma* collected from vegetation, humans, and various animal hosts (25, 53, 68, 125, 126). Transmission is believed to be perpetuated *via* transovarial and transstadial means (127). Largely, molecular tools have been useful in the detection of *R. aeschlimannii* in *Hy. marginatum Aegyptus* collected from Algeria (67) and Morocco (128), and this is one of the common ticks found on cattle in Morocco. Furthermore, this rickettsia has been detected in *Hy. aegyptium* ticks feeding on Algeria tortoise, *Hy. dromedarii, Hy. marginatum rufipes, Hy. impeltatum*, and *Hy. truncatum* collected from cows or camels from Algeria, Sudan, Egypt, and Tunisia (25, 69, 73, 77, 125). Aside from North Africa, *R. aeschlimannii* has been widely detected in blood-fed ticks in West Africa (Mali, Niger, Senegal, Nigeria, Senegal, and Ivory Coast), with a prevalence ranging from 15–95% in several subspecies of *Hyalomma* ticks, including *Hy. marginatum rufipes* and *Hy. truncatum* (52, 68, 74, 76, 78).

Astrakhan fever

Rickettsia conorii subsp. *caspia* is responsible for Astrakhan fever. It was first isolated from a patient in the Astrakhan region located near the Caspian Sea in Russia (9). The clinical manifestation of the disease is similar to that of MSF, except for the absence of a fatal form and a lower incidence of inoculation eschar (9). The first documented isolate of this rickettsia in Africa was obtained from a patient in Chad. The patient had fever, dyspnea, maculopapular rash, inoculation eschar on the leg, and conjunctivitis of the right eye (28). *Rhipicephalus sanguineus* and *Rh. pumilio* have been shown to harbor this rickettsia. In Zambia, the first documented report of

R. conorii subsp. *caspia* engorged *Rh. sanguineus* ticks collected from dog (129). Therefore, further testing of ticks with an emphasis on unfed/un-engorged ticks is needed to clarify whether *Rh. sanguineus* can be infected (by transstadial persistence) and the likelihood of it being a potential vector of *R. conorii* subsp. *caspia*.

Rickettsia massiliae infection

This is another SFG rickettsiae that is infectious to humans, and has been confirmed in Europe, South America, and Africa (8, 130). Patients present with clinical signs similar to MSF (131). In some tropical African countries, *R. massiliae* is associated with several species of *Rhipicephalus*, including *Rh.* spp. from the Ivory Coast (86), *Rh. senegalensis* from Guinea (40), *Rh. guihoni* from Senegal (76), and *Rh. evertsi evertsi* in Nigeria (53).

New rickettsial species infection

Despite the growing number of new species of *Rickettsia* worldwide, data on their complete genomic sequences and annotations are scarce, with only a few species available (3). In recent decades, researchers have characterized several species of bacteria within the genus *Rickettsia* using molecular-based techniques before they can be cultured (41). Uncultured rickettsiae with proper molecular characterization were assigned the nomenclature *Candidatus* (*Ca.*) as proposed by experts according to taxonomic criteria, and is thus considered a potentially new species of *Rickettsia* (132). Numerous cell lines,

media with supplements, and culture conditions have been tested for *in vitro* cultivation of *Rickettsia* spp (133). However, the isolation of these bacteria is challenging (41).

The number of bacteria within the genus *Rickettsia* that fulfilled the criteria for *Ca.* "Rickettsia" spp. continues to increase globally, particularly in Africa. It is important to note that before designating a novel rickettsial species as a strain, additional rickettsial gene analyses are needed. For instance, *Rickettsia* sp. strain Davousti, which was first detected in *Am. tholloni* ticks collected from African elephants in 2007 (134), was further characterized as *Ca.* "Rickettsia davousti," which was conducted—using a tick sample (one *Amblyomma* nymph) from a tourist who travelled from Gabon to Spain in 2015—by targeting five genetic gene fragments used to classify rickettsia partial gene sequences namely *ompB, ompA*, 16S rRNA, *sca4*, and *gltA* (135). Figure 1 provides an overview of the geographical distribution of the SFG *Rickettsia* species reported across Africa.

Furthermore, according to Buysse and Duron (136), before a species can be designated as a novel *Rickettsia* species, there must be a substantial magnitude of difference in their allelic profiles, and there must be a unique relative to all other recognized and putative species within the genus *Rickettsia*. These criteria must be met when a novel pathogen is typed using at least four gene-coding fragments already enumerated (137, 138). It remains to be seen if most studies reporting the existence of novel putative species of *Rickettsia* have fulfilled these criteria. From our literature review, some of these lapses
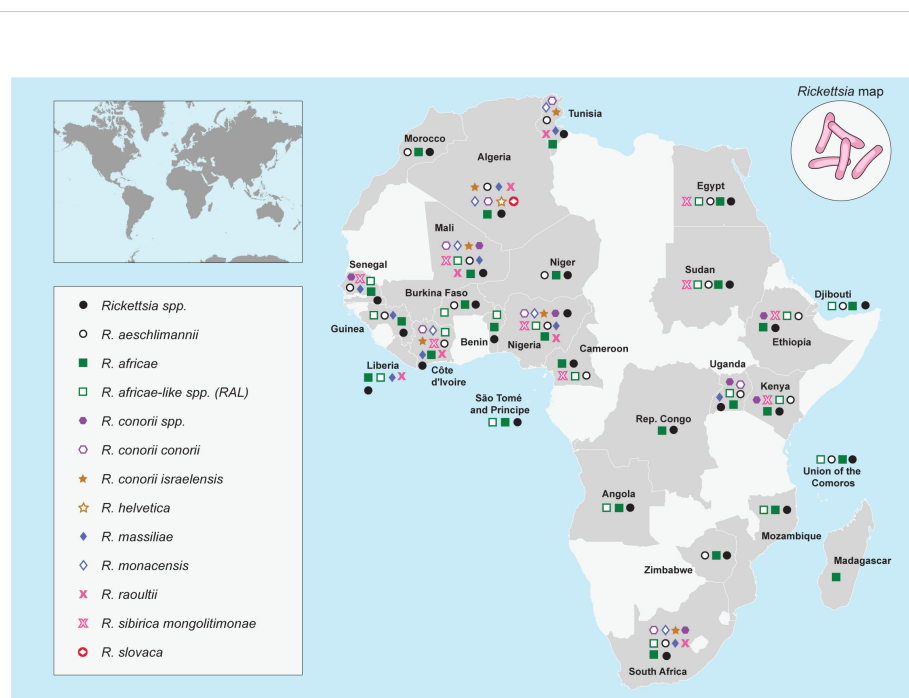

FIGURE 1
Geographical distribution of *Rickettsia* species reported across Africa.

were not fulfilled; however, it is beyond the scope of this review to discuss the downsides of these studies. Based on this evidence, it is likely that most of these new species may be a new genotype of the already characterized species. Reports of new species of *Rickettsia* are mostly based on inadequately performed phylogenetic analyses.

Ticks as competent vectors and reservoirs of SFG *rickettsia* in Africa

The concept "vector competence" can be defined as the intrinsic ability of an arthropod to transmit infection, comprising the efficiency to become infected and to maintain and transmit a pathogen (139). The vector competence of an arthropod can only be determined by feeding the supposed vector on a vertebrate host with the circulating pathogen; thereafter, allowing the arthropod to molt and re-feed on an uninfected susceptible vertebrate host, and finally examining the presence of infection in the latter host (140). Therefore, the mere report of *Rickettsia* DNA detection in blood-fed ticks does not denote vector competence but may simply imply that the genetic material was acquired from the fed blood of the vertebrate host. In addition, pathogen detection in adult ticks may be the result of previous infections at an immature stage. However, this reflects the successful transmission of the pathogen, which, to my knowledge, is the first step of transmission to be tested when investigating vectorial competence in ticks. It is important to emphasize that reports of ticks harboring *Rickettsia* species must not be interpreted as competent vectors. Additionally, pathogen detection in adult ticks collected from non-pathogen-carrying hosts could still be acquired from hosts at immature stages and not from the vertebrate host from which the adult ticks were harvested (10).

Hematophagous arthropods such as lice, mites, and fleas are responsible for the transmission of rickettsial diseases through their infectious feces, unlike ticks, where the bacteria are transmitted primarily *via* salivary secretions (141). These arthropods acquire bacteria either by co-feeding, that is, when uninfected and infected arthropods feed together on the same host (usually bacteremic), or by vertical transmission (142, 143). For an arthropod vector called a bacterial reservoir, rickettsiae in the arthropod can be perpetuated efficiently both transovarially and transstadially (144). As our review focuses mainly on ticks, our discussion will be limited to this group of arthropods. Therefore, transmission occurs through transdermal inoculation *via* tick saliva (4). These ticks can act both as vectors and sometimes as reservoirs of SFG rickettsiae and transmit the infection to domestic animals, humans, and wildlife (145). Most ticks require optimal environmental conditions, hosts, and biotopes. These factors determine the geographical dispersal of ticks and, consequently, the risk of the disease (8).

More than 900 species of ticks are currently recognized, which can be divided into three families: Ixodidae (hard ticks), Argasidae (soft ticks), and Nuttalliellidae (144, 146). The use of several hosts and different life stages, their long life span, and the use of intracellular digestion facilitate the penetration of rickettsia into tick tissues, which enhances the vectorial capacity of ticks. Recently, *Rickettsia* spp. has been discovered in different hosts, among which hard ticks (Ixodidae) remain the main arthropod hosts (18, 147). However, only a few *Rickettsia* species have been documented from a handful of soft ticks (Argasidae). *Rickettsia* species, including *R. bellii* and *Rickettsia hoogstraalii*, are regularly identified in *Argas* and *Ornithodoros* spp (136). Other species, including "*Candidatus* Rickettsia nicoyana," "*Candidatus* Rickettsia wissemanii," *Rickettsia japonica* strain *argasii*, and *Rickettsia lusitaniae* are known from a few *Ornithodoros* and *Argas* species (137, 148–151). Numerous reports on the discovery of new putative species of *Rickettsia* in soft ticks have been documented across Africa. Some of these new species may be closely related to well-known species (152).

The geographical distribution of tick species implicated in the dissemination of the spotted fever group rickettsiae across Africa is shown in Figure 2.

Ixodidae (hard ticks)

Amblyomma

Amblyomma variegatum and *Am. hebraeum* are the main competent tick vectors that transmit *R. africae* and are well-distributed in SSA (78). All parasitic stages (adults, nymphs, and larvae) may transmit *R. africae*. Adult ticks rarely feed on humans, although nymphs attach more frequently, whereas larvae are serious pests (76, 153). The adult stage of *A. variegatum* frequently attacks cattle, but other domestic hosts include sheep, donkeys, horses, pigs, buffaloes, antelopes, and giraffes (153). Unlike other ticks, *Am.* spp. does not just wait passively for their victims on vegetation but are more aggressive, emerging, and running toward a nearby host (153). These tick species are highly responsive to CO_2 concentration, humidity, NH_3, aromatic chemicals, body temperature, and airborne vibrations (95). *Amblyomma variegatum* ticks are life-long reservoirs of *R. africae* (88) because of their transovarial and transstadial perpetuations (142), high transovarial and transstadial transmission rates (100%), and a filial infection rate of 93% in transmission experiments (142). *Rickettsia africae* has also been reported in other species of *Amblyomma* including *Am. compressum* in the Democratic Republic of Congo and Liberia (39, 40), *Am. cohaerens* in Ethiopia (126, 154), *Am. gemma* in Kenya, Burkina Faso, and Ethiopia (41, 126, 155), and *Am. lepidum* in Djibouti, Sudan, and Ethiopia (69, 154, 156). It has been speculated that *Am. cohaerens* may play a role
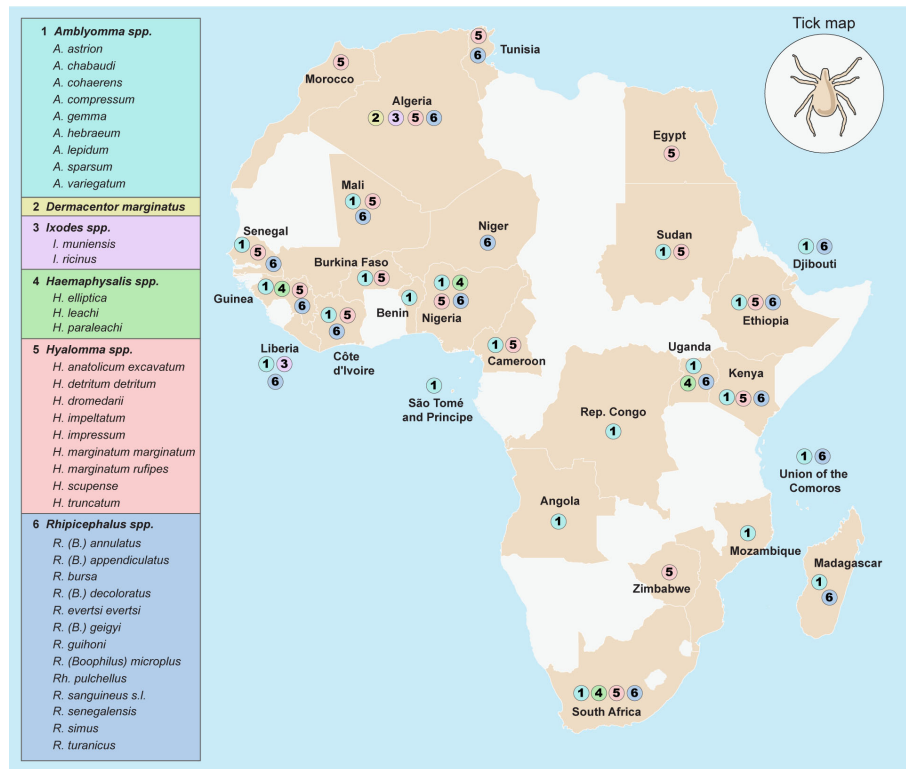
FIGURE 2
Geographical distribution of tick species implicated in the dissemination of Spotted Fever Group rickettsiae across Africa.

in maintaining the natural transmission cycle of *R. africae* in areas with low prevalence of *Am. variegatum* (38).

Hyalomma

Tick species within this genus, especially *Hy. dromedarii* (157, 158), *Hy. impeltatum*, *Hy. excavatum* (159, 160), *Hy. aegyptium* (119), *Hy. impressum*, and *Hy. marginatum rufipes* (77), are vectors as well as potential reservoirs for spotted fever *Rickettsia* including *R. aeschlimannii*, *R. africae* and *R. sibirica mongolitimonae*. *Hyalomma* spp. are aggressive and bite humans (76). Data from numerous epidemiological studies may support the theory that *Hy.* is the vector and reservoir of *R. aeschlimannii* (25, 53, 68, 125, 126). This characteristic could facilitate the transmission of *R. aeschlimannii* to camel handlers and other livestock workers. Several species exist across Africa, with major concentrations occurring in the Mediterranean region and North Africa. *Hyalomma marginatum marginatum*, known as the Mediterranean *Hyalomma*, accounts for 42% of ticks collected from cattle in Morocco (4). This tick species readily bites people using an attack strategy by emerging from their habitat and running toward their perceived hosts when they appear nearby (127). The geographical distribution of tick species may coincide with the distribution of *R. aeschlimannii*

because this bacterium is transmitted transovarially with huge epidemiological significance, as *Hy. marginatum marginatum* may be a reservoir and vector (127). *Hyalomma marginatum rufipes* ticks are widespread and exist only in SSA, and their geographic distribution coincides with *R. aeschlimannii*, which has been shown to be transstadially perpetuated in this tick. *Hy. dromedarii* is widely distributed in Asia and Africa. This tick species can be found in multiple biotopes and a wide variety of hosts (25). Other species of *Hyalomma* that are considered probable vectors include *Hy. truncatum, Hy. impeltatum*, and *Hy. impressum*. *Rickettsia africae* DNA has been reported in some species of *Hyalomma* ticks including *Hy. marginatum rufipes* in Guinea (40) and *Hy. impeltatum* in Nigeria (53).

Rhipicephalus

One of the most widespread ticks with specialized feeding on domestic dogs worldwide is *Rh. sanguineus sensu lato*. This tick is considered a significant vector, as many pathogens, including bacterial and parasitic microorganisms, can replicate inside it (161). This tick species is adapted to warm climates but thrives well in human homes, dog kennels, and cooler regions (162). *Rhipicephalus sanguineus*, a brown dog tick, is thought to be a vector of MSF (163). This hypothesis is supported when humans

are inoculated with crushed *Rh. sanguineus* ticks, and contracted MSF (99). The infectious agent in the tick was described by Brumpt with the name *R. conorii* given in honor of the work of Conor (145, 164). In Western Africa, *R. africae* has been reported in several species of *Rhipicephalus* including *Rh. annulatus* in Nigeria, Guinea, and Senegal (40, 53, 76); *Rh. decoloratus* in Nigeria (165); *Rh. geigyi* in Liberia (40). The vectorial capacity of *Rhipicephalus* ticks for the transmission of *R. africae* remains unclear. However, *Rh. guihoni* is commonly observed in the drier areas of SSA. It is a member of *Rh. sanguineus* group and infests a wide range of hosts, including birds. In addition, ticks of the *Boophilus* subgenus *Rhipicephalus* exhibit monotropic behavior. *Rickettsia africae* has been detected in a handful of closely related species, such as *Rh. (B.) microplus*, *Rh. (B.) decoloratus*, *Rh. (B.) annulatus*, and *Rh. Geigyi* (48, 51, 54).

Argasidae (soft ticks)

Some SFG and TGR rickettsiae have been reported in argasid ticks (166). However, the host range, pathogenicity, and distribution of *Rickettsia* spp. Associated with argasid ticks are poorly understood. In Zambia, *R. lusitaniae* was detected in *Ornithodoros faini* recovered from bat guano in Lusaka, and *R. hoogstraalii* in *Argas* (*Ar*) *walkerae* ticks obtained from a chicken coop in Isoka (167). Interestingly, *R. lusitaniae* has also been detected in three other continents namely Europe, Asia, and the United States. *Ornithodoros faini* is a bat-associated tick in Africa; however, the role of vertebrate hosts in the maintenance cycle of *R. lusitaniae* remains largely unknown. Nonetheless, a human case of borreliosis transmitted by *O. faini* was recently reported in Zambia (167). Therefore, transmission studies are needed to investigate the vectorial capacity of *O. faini* and pathogenicity of *R. lusitaniae* in humans and animals. On the contrary, *Ar. walkerae*, a known poultry tick, is closely associated with *R. hoogstraalii*, a suspected member of SFG rickettsiae with unknown pathogenicity, and is closely related to *R. felis*, an emerging pathogen transmitted by fleas (168). Currently, *R. hoogstraalii* is not known to cause diseases in vertebrates, but it has been observed to exhibit cytopathic effects on mammalian cells, similar to pathogenic SFG rickettsia (169). Originally, *R. hoogstraalii* was reported in Croatia in *Hae. sulcata*, an ixodid tick (170). Additionally, other argasid ticks, including *Ornithodoros capensis* and *Ar. persicus*, have been shown to harbor rickettsial bacteria across diverse geographical spaces (167). In general, *Hae. sulcata, O. capensis*, and *Ar. persicus* are bird-associated ticks. The migratory birds may have contributed to the wide distribution of *R. hoogstraalii* in southern Africa, including Zambia. In Namibia and South Africa, *R. hoogstraalii* has also been reported in *Argas transgariepinus* ticks collected from bats (149, 171). In Zambia, warthog-feeding soft ticks (*Ornithodoros porcinus*)

were found to harbor *R. lusitaniae* after analyzing the *glt*A and *htr*A nucleotide sequences (172). In Ethiopia, *R. hoogstraalii* DNA was detected in *Ar. persicus* collected from cracks and crevices of human dwellings and under the bark of trees in the vicinity of livestock areas (173). Its high infection rate in ticks suggests that it may be a tick symbiont. Soft ticks belonging to the *Ornithodoros erraticus* complex, including *Ornithodoros occidentalis*, *O. erraticus*, and *Ornithodoros normandi*, have been reported in northern Africa (136). Both *O. occidentalis* and *O. normandi* are known only from North Africa and have been reported from Morocco and Algeria, respectively, whereas the last species, *O. erraticus*, is more widespread across the Mediterranean regions (136). Small mammals are the preferred hosts for this tick, but they can also bite humans (174). These ticks have been found to carry some potential pathogenic *Rickettsia* namely "*Candidatus* Rickettsia africaseptentrionalis" and "*Candidatus* Rickettsia mauretanica." These novel *Rickettsia* species belong to a transitional phylogenetic group and are closely related to *Rickettsia asembonensis* (175).

Geographical distribution and epidemiological relationship between SFG rickettsiae and tick vectors across different regions in Africa

Several species of SFG rickettsiae infect both humans and animals worldwide. Some rickettsial pathogens are prevalent in a particular geographic region and are largely dependent on the distribution of competent tick vectors. SFG rickettsiae, which are considered human pathogens, have been reported in Africa and include *R. africae, R. aeschlimannii, R. conorii, R. sibirica mongolitimonae, Rickettsia slovaca, Rickettsia helvetica, R. massiliae, Rickettsia monacensis*, and *Rickettsia raoultii* (176). A bibliographic list of some SFG rickettsiae in different tick vectors distributed across different countries in Africa is summarized in Table 2.

West Africa

The Economic Community of West African States (ECOWAS) comprises 15 member states, including Benin, Burkina Faso, Cape Verde, Cote d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, and Togo. Several nations within the ECOWAS sub-region have reported the presence of SFG rickettsiae, such as Nigeria (53, 165), the Benin Republic (55), Niger and Mali (56, 78), Liberia and Guinea (40), Cote d'Ivoire (52), and Senegal (57). Most tick species harboring SFG rickettsiae in

TABLE 2 Bibliographic reports of rickettsiae in hard ticks in Africa according to tick species and country.

Rickettsia aeschlimannii

Tick species	Country	Reference
Amblyomma variegatum	Nigeria	(53)
Hyalomma aegyptium	Algeria	(125)
Hyalomma anatolicum excavatum	Algeria	(64)
Hyalomma detritum	Algeria	(125)
Hyalomma dromedarii	Algeria, Egypt, Sudan, Tunisia, Nigeria	(68–71, 73, 77)
Hyalomma excavatum	Algeria	(177)
Hyalomma impeltatum	Egypt, Senegal, Tunisia, Algeria, Nigeria	(57, 68, 70, 73, 74, 178, 179)
Hyalomma marginatum	Algeria, Egypt, Morocco, Sudan, Kenya, Algeria	(67, 69, 75, 128, 177–179)
Hyalomma rufipes	Algeria, Burkina Faso, Chad, Egypt, Ethiopia, Mali, Niger, Republic of Djibouti, Senegal, Sudan, Zimbabwe, Cameroon, Kenya, Nigeria	(41, 42, 50, 56, 57, 68, 71, 73–77, 79, 126, 144)
Hyalomma scupense	Algeria	(64, 179)
Hyalomma truncatum	Burkina Faso, Ethiopia, Kenya, Sudan, Senegal, Cameroon, Mali, Nigeria	(41–43, 50, 56, 68, 69, 76, 126, 155)
Rhipicephalus (Boophilus) annulatus	Kenya, Nigeria	(53, 155)
Rhipicephalus appendiculatus	South Africa	(124)
Rhipicephalus evertsi evertsi	Senegal, Nigeria	(53, 57, 76)
Rhipicephalus pulchellus	Kenya	(42, 43)
Rhipicephalus sanguineus (sensu lato)	Mali	(56)

Rickettsia africae

Tick species	Country	Reference
Amblyomma astrion	Sao Tome and Principe	(37)
Amblyomma chabaudi	Madagascar	(180, 181)
Amblyomma cohaerens	Ethiopia	(38, 126, 154)
Amblyomma compressum	Liberia, Republic of Congo	(39, 40)
Amblyomma eburneum	Kenya	(182)
Amblyomma gemma	Ethiopia, Kenya and Burkina Faso, Uganda, Kenya	(41–44, 126, 155, 183)
Amblyomma hebraeum	Kenya, South Africa	(46, 47, 61, 155, 184)
Amblyomma lepidum	Ethiopia, Republic of Djibouti, Sudan, Kenya	(43, 48, 69, 78, 79, 154, 156)
Amblyomma sparsum	Kenya	(42)

(Continued)

TABLE 2 Continued

Rickettsia africae

Tick species	Country	Reference
Amblyomma spp.	Uganda	(183)
Amblyomma variegatum	Angola, Burkina Faso, Burundi, Ethiopia, Guinea, Kenya, Liberia, Madagascar, Mali, Senegal, Republic of Djibouti, Niger, Nigeria, Sudan, Uganda, Union of the Comoros, Cameroun, Uganda, Madagascar, Sao Tome and Principe, Benin republic, Ivory Coast, Mozambique	(37–42, 48–52, 54–57, 59, 62, 63, 69, 76, 78, 79, 126, 154, 155, 165, 181, 183, 185–189)
Haemaphysalis paraleachi	Guinea	(40)
Hyalomma aegyptium	Algeria	(190)
Hyalomma detritum	Algeria	(190)
Hyalomma dromedarii	Algeria, Egypt, Tunisia, Sudan	(70–72, 178)
Hyalomma impeltatum	Algeria, Egypt, Tunisia, Ivory Coast	(54, 70, 72, 178)
Hyalomma impressum	Ivory Coast	(52)
Hyalomma marginatum	Egypt, Ivory Coast	(52, 178)
Hyalomma rufipes	Guinea, Senegal, Sudan, Benin republic	(40, 56, 57, 71)
Hyalomma truncatum	Kenya, Benin republic, Ivory Coast	(52, 56, 155)
Rhipicephalus (Boophilus) annulatus	Kenya, Djibouti, Senegal	(48, 76, 155)
Rhipicephalus (Boophilus) decoloratus	Ethiopia, Guinea, Nigeria, Uganda, South Africa, Ivory Coast	(40, 54, 82, 126, 154, 165, 183, 184)
Rhipicephalus (Boophilus) geigyi	Liberia, Ivory Coast	(40, 54)
Rhipicephalus (Boophilus) microplus	Union of the Comoros, Madagascar, Benin republic, Ivory Coast	(51, 52, 54, 56, 181)
Rhipicephalus appendiculatus	Union of the Comoros, Kenya, Uganda, South Africa	(42, 51, 61, 155, 184)
Rhipicephalus evertsi evertsi	Senegal, Kenya, Ethiopia, Benin republic, South Africa	(42, 56, 61, 76, 82, 184)
Rhipicephalus maculatus	Kenya	(182)
Rhipicephalus pulchellus	Kenya	(155)
Rhipicephalus sanguineus (*sensu lato*)	Nigeria, Ivory Coast	(54, 165)
Rhipicephalus spp.	Kenya	(183)

R. conorii subspecies caspia

Tick species	Countries	Reference
Rhipicephalus sanguineus (*sensu lato*)	Zambia	(129)

(Continued)

TABLE 2 Continued

Tick species	Countries	Reference
Haemaphysalis leachi	Uganda	(66)
Rhipicephalus evertsi evertsi	Senegal	(76)
Rhipicephalus sanguineus (*sensu lato*)	Algeria, Morocco, Tunisia, Nigeria	(85, 103, 191–193)

Rickettsia coronii subsp Israelensis

Tick species	Countries	Reference
Amblyomma spp.	Kenya	(155)
Rhipicephalus appendiculatus	Cameroon	(50)
Rhipicephalus sanguineus (*sensu lato*)	Nigeria, Tunisia	(65, 85, 191)

Rickettsia Helvetica

Tick species	Countries	Reference
Hyalomma impeltatum	Tunisia	(70)
Ixodes ricinus	Algeria, Tunisia	(81, 194)

Rickettsia massiliae

Tick species	Countries	Reference
Haemaphysalis leachi	Uganda	(66)
Haemaphysalis paraleachi	Guinea	(40)
Rhipicephalus senegalensis	Ivory Coast, Guinea	(40, 52)
Rhipicephalus bursa	Algeria	(64, 179)
Rhipicephalus evertsi evertsi	Nigeria	(53)
Rhipicephalus guilhoni	Senegal	(76)
Rhipicephalus lunulatus	Cameroon	(50)
Rhipicephalus praetextaatus	Ethiopia	(126)
Rhipicephalus sanguineus (*sensu lato*)	Tunisia, Algeria, Morocco	(84, 85, 103, 179, 191, 193, 195)
Rhipicephalus turanicus	Tunisia	(84)

Rickettsia monacensis

Tick species	Countries	Reference
Hyalomma impeltatum	Tunisia	(70)
Ixodes ricinus	Algeria, Morocco, Tunisia	(81, 103, 194, 196)
Rhipicephalus sanguineus (*sensu lato*)	Tunisia	(84)

(Continued)

TABLE 2 Continued

Rickettsia monacensis

Tick species	Countries	Reference
Rhipicephalus turanicus	Tunisia	(84)
Rhipicephalus turanicus	Tunisia	(84)

Rickettsia raoultii

Tick species	Countries	Reference
Ixodes muniensis	Liberia	(76)
Rhipicephalus appendiculatus	South Africa	(83)
Rhipicephalus sanguineus	South Africa	(83)

Rickettsia sibirica mongolitimonae

Tick species	Countries	Reference
Amblyomma gemma	Kenya	(155)
Hyalomma truncatum	Cameroon, Mali, Senegal	(50, 56, 76)

Rickettsia slovaca

Tick species	Countries	Reference
Dermacentor marginatus	Algeria	(64, 81)
Haemaphysalis punctata	Algeria	(64)

West Africa belong to the genera *Amblyomma* (55, 56), *Rhipicephalus* (56, 86), and *Hyalomma* (56, 68, 74).

Rickettsia africae was highly prevalent in *A. variegatum* ticks across the sub-region (40, 52, 57). Other tick genera where *R. africae* has been reported with lower prevalence include *Hyalomma* and *Rhipicephalus* (52, 56, 76), which suggests that they are probably not competent vectors (52). In contrast, *Rickettsia aeschlimannii* has been observed in *Hyalomma* ticks, with a higher prevalence in *Hy. marginatum rufipes* than in *Hy. truncatum* in Mali (56, 78), Senegal (76), and the Ivory coast (52). Similarly, *R. sibirica mongolitimonae* was observed in *Hy. truncatum* from Niger (78), Senegal (76), and Mali (56). Interestingly, fragments of *R. massiliae* DNA have been detected in *Rh.* spp. ticks collected on the Ivory Coast (86) and Mali (78), as well as in *Rh. senegalensis* in Liberia (40), *Rh. guihoni* in Senegal (76), and *Hae. paraleachi* ticks collected in the Republic of Guinea (40). *R. conorii israelensis* was also observed in *Rh. sanguineus sensu lato (s.l.)* in Nigeria (65), whereas *R. conorii* ssp. has been reported in *Rh. evertsi evertsi* ticks from Senegal (76). Sporadic reports of *R. raoultii* have been documented in South Africa in *Rh. sanguineus s.l.* (45, 83), and *Rh.* spp. (83), and only one report in *I. muniensis* ticks from Liberia (40).

North Africa

According to the United Nations, North Africa includes eight territories or countries (Algeria, Libya, Sudan, South Sudan, Egypt, Tunisia, Morocco, and Western Sahara) that are found in the northernmost area of the African continent. Since the beginning of the 21st century, the SFG *Rickettsia* has been found in North Africa. Since then, several SFG rickettsiae have been detected in arthropods thanks to the use of PCR and sequencing methods leading to new questions with regards to the geographical distribution of rickettsiae in this region.

To date, eight tick-borne rickettsial species have been detected in North Africa, mainly in human cases or ticks. These included *R. conorii* subsp. *conorii*, *R. conorii* subsp. *israelensis*, *R. aeschlimannii*, *R. sibirica mongolitimonae*, *R. massiliae, R. slovaca, R. raoultii*, and *R. monacensis* (81, 84, 125, 181). In Algeria, both *R. conorii* subsp. *conorii* (MSF) (97) and *R. aeschlimannii* (123) have been associated with human rickettsiosis. *Rickettsia conorii* subsp. *israelensis* was detected in *Rh. sanguineus* ticks in Tunisia (197), suggesting that the geographical distribution of this species is broader than expected. Additionally, *R. aeschlimannii* infection has been

confirmed in *Hy. dromedarii* ticks in Tunisia (25), Egypt (73), and Sudan (69). In Algeria, *R. aeschlimannii* has been reported in *Hy. aegyptium* (125), *Hy. anatolicum excavatum*, and *Hy. scupense* (64). Documented human cases of *R. aeschlimannii* have been reported in Morocco (121), Tunisia (122), and Algeria (123). MSF has been reported in human patients in Algeria (181).

Rickettsia slovaca, a member of the SFG rickettsiae common in Europe, has also been isolated from ticks, such as *D. marginatus* (64, 81) and *Hae. punctata* (64). *Rickettsia massiliae* has been detected in *Rh. turanicus* and *Rh. sanguineus s.l.* ticks collected from livestock in Tunisia (70, 84, 197), Morocco (103), and Algeria (67). Similarly, *R. monacensis* DNA was detected in *Rh. sanguineus s.l.* tick specimens were collected from goats in Tunisia (84).

East Africa and Central Africa

Numerous tick-borne zoonotic and veterinary diseases have been documented in East Africa, including SFG rickettsiaeca used by *R. africae*, *R. conorii*, and *R. aeschlimanii* (58, 126, 182, 186, 198). Extensive studies have been conducted in Kenya on *R. africae* in ticks collected from vertebrate animals, particularly cattle. The results indicated a high prevalence of *R. africae* across several counties within the country (42, 43, 155, 186, 187). High prevalence of *Rickettsia* spp. infection in Kenya was attributed to the presence of a high population of domestic (cattle, sheep, goats, and camels) and wild (giraffes, buffaloes, and rhinoceroses) animals, which predominantly feed on these animals and acquire *Rickettsia* spp. infections (43). Furthermore, PCR and sequencing revealed the presence of *R. africae* DNA in several tick species within the genera *Amblyomma*, *Rhipicephalus*, and *Hyalomma* (43, 155, 185–187). Furthermore, *R. massilliae* was registered in *Rh. annulatus*, *R. conorii* subsp. *Israelensis* in *Amblyomma* ticks, and *R. mongolitimonae* in *Am. gemma* (155). Using PCR and sequencing of three target genes (*glt*A, *omp*A, and *omp*B), *R. aeschlimannii* has been detected in *Hy. truncatum* and *Hy. marginatum* (43).

The first documented report of *R. africae* in Djibouti was in 2007 on *Am. lepidum* ticks collected from cattle imported from Ethiopia (78). In addition, *R. africae* was detected in *Am. lepidum*, *Am. variegatum*, and *Rh. annulatus* from Djibouti (48). Additionally, *R. aeschlimanii* was amplified in *Hy. truncatum* and *Hy. marginatum* ticks (48). In Ethiopia, *R. aeschlimannii* has been reported in *Hy. rufipes* and *Hy. truncatum* ticks (79, 126). *R. massiliae* has also been documented in *Rh. praetextatus* ticks (126). *R. africae* DNA has been reported in *Am. lepidum* (79), *Am. variegatum* (38, 79, 126), *Am. cohaerens* (126), and *Rh. decoloratus* in Ethiopia (82, 126). Additionally, in pools of *Amblyomma* and *Rhipicephalus* ticks, *Rickettsia africae* DNA was detected from those collected

in Ethiopia (173). *R. conorii* was detected in *Hae. punctaleachi* ticks (156), whereas both *R. conorii conorii* and *R. massiliae* were detected in *Hae. leachi* and *Rh. praetextatus* ticks (66), with a concomitant high prevalence of *R. africae* in *A. variegatum* ticks (182). In Central Africa, several species of SFG *Rickettsia* have been recorded in ticks collected from this region. For instance, *R. africae* has been reported in *Am. compressum* ticks from the DRC (39). Similarly, *R. africae* has been documented in *Amblyomma* ticks from Cameroon (96) and the (CAR) (188). In Cameroon, different SFG rickettsiae, including *R. africae*, *R. aeschlimannii*, *R. sibirica*, and *R. massiliae*, were detected in *Amblyomma, Hyalomma*, and *Rhipicephalus* ticks (50). Finally, in Chad, *R. aeschlimannii* has been documented in *Hyalomma* ticks (79).

Southern Africa

Southern African Development Community (SADC) member states includes Angola, Botswana, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe. Four major tick-borne SFG rickettsiae associated with human diseases have been reported in southern Africa. These included *R. africae* (87), *R. raoultii* (83), *R. conorii* (164), *R. aeschlimannii* (75), and *R sibirica* subsp. *mongolitimonae* (199). In this region, *R. africae* is primarily transmitted by *Am. hebraeum* (88). Other tick species have been found to harbor *R. africae* (40, 78); however, this bacterium was detected for the first time in *Hae. elliptica*, thereby possibly extending the range of known vectors. The detection of *R. africae* in *Am. hebraeum*, a tick known to readily bite humans, and *Hae. elliptica*, one of the most common ticks infesting domestic dogs in South Africa, underpins the potential risk of human infection with this pathogen in the southern Africa region. *Rickettsia aeschlimannii* was registered as a South African patient after returning from hunting and fishing trips (124). Additionally, *Hy. truncatum* ticks were collected from cattle in Angola (200). Using PCR, *R. africae* and *R. aeschlimannii* were reported in *Am. variegatum* and *Hy. truncatum* ticks collected from dogs and cattle in Shangombo, a town at the Zambia–Angola border (201). Furthermore, both *R. africae* and *R. aeschlimannii* were documented in *Hyalomma* ticks collected from cattle in Zambia (202). In Lesotho, *R. africae* was detected in *Hy. rufipes* and *Rh. evertsi evertsi* ticks collected from domestic animals including cattle, goats, sheep, and horses (203). In addition, *R. africae* was detected in *Am. variegatum* adult ticks from cattle and their questing larvae in South Africa (204), and in *Am. variegatum* and *Am. heabreum* ticks from cattle in Mozambique (205). *Rickettsia conorii* subsp. *caspia* was recorded in *Rh. sanguineus* ticks collected from Zambia (129). Additionally, *Rickettsia raoultii* has been detected in *Rh. sanguineus* ticks collected from cattle and *Rh. appendiculatus* in sheep (83). The detection of this bacteriumin

Island nations

Studies investigating the prevalence of rickettsial DNA in ticks collected from domestic and wild animals have been conducted in the Indian Ocean. In Madagascar, *Amblyomma* ticks are regarded as the predominant tick species, with a high prevalence of *R. africae* (183, 191, 206). Human infections caused by SFG rickettsiae in Madagascar have been previously documented (207). In the Union of Comoros, a prevalence of 90% of *R. africae* in *A. variegatum* ticks has been reported (51). Additionally, other tick species, such as *Rh. appendiculatus* and *Rh. (B.) microplus*, were found to harbor *R. africae* DNA (51). Interestingly, *R. monacensis*, an emerging human pathogen of SFG rickettsiae, has been reported in dogs from Cape Verde (208). This pathogen has been detected in ticks from North Africa, Europe, and Asia, as well as in humans with MSF-like illnesses from Spain and Italy (209–211). Rickettsial DNA has also been detected in *Ar. echinops* ticks in Madagascar (191). The relationship between different SFG rickettsiae and tick species across Africa is represented in the heat map shown in Figure 3.

Epidemiological aspects and challenges

Evolutionary perspective of *Rickettsia* perpetuation

From an evolutionary perspective, if the ancestral group of rickettsial organisms is a symbiont, it is possible that evolution played a major role that led to *Rickettsia* microorganisms finding a way (aside from tick transovarial-transmission) to perpetuate in permanent cycles in ticks (10). The finding of *Rickettsia* species in phylogenetically distant tick species suggests possible horizontal transmission (10). The transmission of *Rickettsia* could also occur *via* tick parasitoids or hyperparasitism (a tick feeding on another tick), as validated for other tick-associated bacteria (212–214). Parasitoids of the genus *Ixodiphagus* (*Ix*) (Hymenoptera: Chalcidoidea: Encyrtidae) are well-known natural enemies of ticks and have been described in many tick species worldwide (215, 216). However, the biology and ecology of these parasitoids remain unclear (217). Furthermore, recent studies have demonstrated the potential role of *Ix. hookeri* in the circulation of certain bacteria, including rickettsiae (*Rickettsia helvetica* and *Rickettsia monacensis*), in ticks (216). Regrettably, there is a critical lack of data on the presence of parasitoid wasps in ticks in Africa. Recently, the existence of *Ix. hookeri*, a parasitic wasp of ticks, was demonstrated in *Rh. s (B.)*

microplus ticks collected in Côte d'Ivoire, west Africa, using molecular based technique (216). The results showed that infestation by parasitoid wasps can occur in adult ticks, with a higher prevalence than previously reported. Many rickettsiae species are endosymbionts; consequently, the level of their dependence on ticks is variable (10). An obligate symbiont may be present in most tick populations; thus, co-cladogenesis between ticks and symbionts should be expected. However, numerous *Rickettsia* species worldwide affect human health, and Africa is no exception.

Role of small mammals, domestic animals, and wildlife in the epidemiology of SFG Rickettsiae

Tick-borne rickettsiosis is among the oldest known vector-borne diseases. In Africa, several species of *Rickettsia* have been detected in vertebrate animals (178). Many domestic (sheep, goat, cattle, and dogs) and wild (rodents, hedgehogs, wild rabbits, and opossums) mammals act as hosts and contribute to the dispersal of *Rickettsia*-carrying ticks in different geographical areas. The role of these mammals in Africa as amplifying hosts for the SFG *Rickettsia* spp. requires further investigation. Domestic animals, including livestock, may play a role in perpetuation of pathogenic rickettsiae (218). Domestic ruminants in endemic areas have demonstrated evidence of exposure to SFG rickettsiae through detection of antibodies using serological tests (192, 219, 220). However, it remains unclear whether these animals show signs of infection or whether they only act as temporary bacterial amplifiers to re-infect ticks. If they do show any signs of bacteremia, further studies are needed to unravel how long this bacteremia lasts before seroconversion. Furthermore, immunological experiments are needed to clarify whether the immune response persists and is protective against reinfection. The prevalence across vertebrate animals ranges from 0–65% in Africa. Variations in seroprevalence rates may reflect geography, ecology, the method of animal handling, and climatic differences that affect the diversity, abundance, and distribution of ticks in particular areas. Due to cross-reactivity, the discrimination of *Rickettsia* spp. using serology is difficult. Serological screening for SFG rickettsiae has been carried out for small ruminants in Nigeria and dogs in Angola using the indirect fluorescent antibody test (IFAT) (59, 192). Dogs may develop rickettsiemia due to *R. conorii* with the development of clinical signs but may not be considered reservoirs of *Rickettsia* spp (189). Therefore, we could consider these animals sentinels to SFG rickettsiae in a particular geographical region (221). Camelids (with particular reference to one-humped camels) appear to be potential hosts for rickettsial species, particularly in Africa. The estimated molecular prevalence was 18.8% in Nigeria (74), 41.0% in Egypt (157), and 2.7% in Tunisia (70).
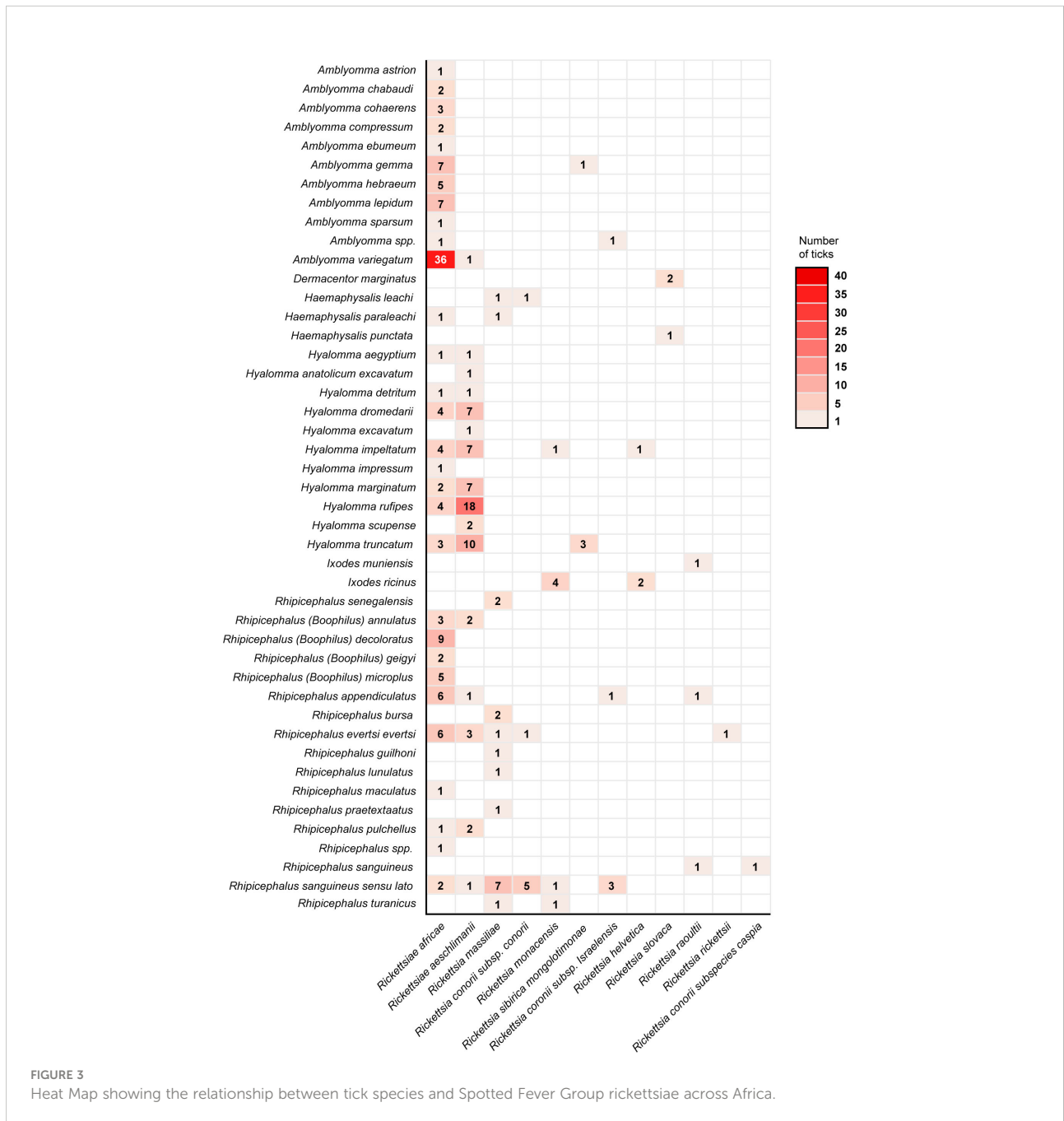
FIGURE 3
Heat Map showing the relationship between tick species and Spotted Fever Group rickettsiae across Africa.

Dogs may play an important role in the epidemiology of SFG rickettsioses in Africa, as they are important hosts of several African tick vectors (13), and could bring infected ticks close to humans, as shown in other parts of the world (222–224). For example, domestic dogs in South America have been shown to act as amplifying hosts of *R. rickettsii* for *Am. aureolatum* ticks (225). Furthermore, advances in molecular diagnostics have illuminated the possible role of small mammals as reservoirs or hosts for numerous emerging and re-emerging infectious agents. This finding is important for understanding the epidemiology of the disease and formulating preventive measures against it (226). Two *Am. variegatum* ticks collected from small mammals in Mali were positive for *R. africae* by PCR (227). Additionally, *R. conorii* DNA has been reported in a pool of *Rh. sanguineus* collected from domestic rodents in Nigeria (226). In another study, rickettsial DNA was detected in 39.8% of

the spleens of vervet monkeys (*Chlorocebus pygerythrus*) from Luangwa National Park, Zambia (58). In another study in South Africa, *R. massiliae* was amplified in *Am. sylvaticum* ticks collected from leopard tortoise (*Chersina angulate*) and *Rh. simus* ticks from Bushveld gerbil (*Gerbilliscus leucogaster*) (228). Furthermore, of the 12 *Am. compressum* ticks collected from pangolins (*Manis gigantea*) in the Republic of Congo, 50% were positive for SFG rickettsiae with 100% homology to *R. africae* (39). *Rickettsia africae* was detected at a high prevalence of 100% in *Am. chabaudi* ticks collected from Malagasy spider tortoises (*Pyxis arachnoides*) (206). In Algeria, *Rh. sanguineus* ticks collected from wild mammals [boars (*Sus scrofa algira*), jackals (*Canis aureus*), and mongoose (*Echinomon herpestis*)], and screened for *Rickettsia*, revealing the presence of *R. massiliae* (64). In addition, *R. sibirica mongolitimonae* was found in adult *Hy. aegyptium* ticks collected from spur-thighed tortoises (*Testudo graeca*) in Algeria (119).

Role of avian populations in the epidemiology of SFG *Rickettsia*

Research on the possible role of avian populations in the epidemiology of rickettsiosis in Africa is still in its early stages. Surveys for *Rickettsia* infection in birds in Africa are scarce, with a focus on the detection of rickettsiae in ticks collected from birds. In Africa, antibodies against SFG rickettsiae were detected in farmed ostriches (*Struthio camelus*) in Zimbabwe (87). It was speculated that the detected antibodies could be specific to *R. africae*, as this rickettsial species was identified in *Am. hebraeum* ticks that usually parasitize ostriches in Zimbabwe. However, it is still possible that it could be other SFG rickettsiae, especially *R. conorii*, as it was reported circulating in that area at that time. Most studies on *Rickettsia* on wild birds have been conducted in Europe and America (154, 229, 230). Of the 140 ticks collected from one dunnock (*Prunella modularis*) and five robins (*Erithacus rubecula*), 61 *Hae. concinna* and *I. ricinus* ticks were PCR-positive for *R. helvetica* and 11 *I. ricinus* ticks were PCR-positive for *R. monacensis* (154). Furthermore, no correlation was observed between the positive PCR ticks tested and blood DNA from the birds. In addition, rickettsemia in avian hosts persists after the ticks have been detached; however, the possible role of birds as amplifying hosts was dismissed, as transmission of rickettsia is possible from ticks to birds, but the reverse rarely occurs (154, 231). As most of these birds are migratory, most of which pass through many parts of Africa to avoid the harsh winter and breed, further studies should be advocated to possibly trap some of these birds and screen both the birds and accompanying vector ticks for SFG rickettsiae.

The potential of domestic dogs to act as primary hosts for the adult stage of *Am. aureolatum* in Brazilian spotted fever (BSF) endemic areas has been evaluated (225). In South America, Binder et al. (225) did not consider passerine birds

to play any role in amplifying the hosts of *R. rickettsii* for *Am. aureolatum* ticks, although this group of birds is a major host for immature stages of the tick vector. This statement relies on previous studies that failed to detect rickettsemia or tick-rickettsial acquisition among *R. rickettsii*-exposed passerines (225). Indeed, the high body temperature of birds (> 40°C) should be interpreted as a natural barrier for rickettsial survival in this vertebrate group, as there are no reports of the *in vitro* growth of any *Rickettsia* species at temperatures above 37°C.

Tick-borne rickettsioses among travelers and challenges in surveillance of spotted fever rickettsial infection

Owing to globalization, people can cross borders worldwide, and this phenomenon has led to interchanging the epidemiologic burden from each region (232). Tourism-related activities represent a source of income for developing countries, and international adventure tourism has increased astronomically in recent years. Data available from the Geosentinel surveillance network showed that approximately 280 returning travelers from 1996 to 2008 had reported rickettsial diseases, with a considerable proportion of these individuals with SFG rickettsioses (21). Measures to protect wild fauna and biodiversity in combination with land rehabilitation and management practices, including forestry, increase the potential for exposure to arthropods and the risk of rickettsial transmission (27). During travel, humans may wander into previously untouched tick habitats, resulting in an increased risk of tick bites, predisposing them to tick-borne infections (92). SFG rickettsiae transmitted by ticks account for the majority of ricketsioses among travelers, with several cases of ATBF (*R. africae*) among travelers from SSA (92). The two main tick vectors are *Am. variegatum* and *Am. hebraeum*, which are usually found to have high rates of infection (> 50%) in nature (11, 233).

Travelers returning from SSA are at an increased risk of rickettsial infections caused by tick-borne spotted fever than those caused by dengue or typhoid fever (20). In SSA, rickettsial diseases in international travelers are the second most commonly diagnosed diseases associated with patients with systemic febrile illnesses (20, 232). A recent systematic review showed that over 100 confirmed clinical cases of ATBF (due to *R. africae*) have been documented in European travel, accounting for over 80% of the registered cases (234). Notably, at least 70% of clinical *R. africae* cases have altered laboratory parameters, with an increase in transaminases and C-reactive protein being the most important changes (234).

In the last ten years, cases of ATBF have been documented in travelers returning from southern Africa, with more cases from patients returning from South Africa (235–237) and Zimbabwe (93, 235). Other reports include travelers returning from Uganda (238), Kenya (239), and Tanzania (240). The majority of the patients were men with a mean age of 40 years, while there were

children with ages ranging from 7–16 years (92). Additionally, the majority of the patients were originally from Europe (95, 232, 241), while patients from the United States (93, 241, 242), South America (243, 244), and Asia (245, 246) have also been reported. An overview of some of the published cases of ATBF from 2010 to date is summarized in Table 3. The clinical symptoms displayed by these patients were consistent with those previously reported for ATBF, including eschars and maculopapular rash. Notably, the affected patients shared the risk factors of either game-hunting safari or walking in a rural game-hunting reserve. This observation was made following a seroepidemiological study on returning Norwegian travelers (88). Nonetheless, the diagnosis of most patients with clinical ATBF was performed by PCR detection of *R. africae* using tissue biopsy or swabs (92).

The clinical presentation and severity of SFG rickettsiosis are highly variable (257), but clinical diagnosis can be easy in patients from endemic regions with a history of tick bites and other accompanying symptoms such as fever, skin rash, and

headache during summer and spring months (258). Current methods for rickettsial diagnosis and disease surveillance require major overhaul, because even experienced epidemiologists and clinicians have challenges in consistently and accurately confirming or eliminating the diagnosis of SFG rickettsioses. Importantly, some cases of SFG rickettsiosis may occur during off-season periods in endemic areas (259), in locations where SFG rickettsiosis is unknown to medical practitioners (260), or even in travelers who have not declared their recent travel history (258).

The diagnosis of clinical infections due to SFG rickettsiae is still based on serological testing, despite advances in molecular technologies, because of the need for convalescent antibody titer testing, which is rarely undertaken (261). Early treatment of patients might decrease the expected rise in convalescent IFAT endpoint titers or stop the appearance of skin rash or other symptoms that are peculiar to suspected SFG rickettsiosis and consequently reduce the severity and duration of illness (262). In addition, rickettsiae microorganisms do not multiply

TABLE 3   Summary of case reports describing African Tick Bite Fever (ATBF) among travelers from 2010 to date.

Year	Sex	Age	Nationality	Country of travel	Purpose of travel	References
2010	NA	NA	Switzerland	South Africa	Walk in a game park	(95)
2012	M	60	Portugal	South Africa	Safari	(232)
2012	F	52	United States of America	Zambia & Botswana	Work & Safari	(247)
2012	F	61	Japan	South Africa	Safari	(245)
2013	M	45	Poland	South Africa	Safari	(248)
2013	M	47	Germany	South Africa	Safari	(249)
2014	F	40	Italy	Zimbabwe	Medical Doctor dispensary	(93)
2014	M	76	United States of America	South Africa	Hunting	(250)
2015	M	63	United States of America	South Africa	Safari in a game reserve	(241)
2015	M F	53 51	Netherlands	South Africa	Safari	(139)
2015	M	66	France	South Africa	–	(251)
2015	F	15	United States of America	South Africa	Game hunting	(242)
2015	M	51	Poland	South Africa	Safari	(252)
2016	F	67	Canada	Africa (not specified)	Safari	(94)
2016	F	30	Austria	Tanzania	–	(240)
2016	F	67	United States of America	Africa	Game hunting	(94)
2016	M	30	United States of America	Kenya	Safari	(239)
2016	M	29	Slovenia	Uganda	–	(238)
2017	M	56	Sweden	South Africa	Safari	(237)
2017	M	41	Sweden	Zimbabwe	Visiting rural environment	(237)
2017	M	7, 8 and 16	Spain	South Africa	Game hunting & Safari	(235)
2017	M	51	Canada	South Africa	Game hunting & Safari	(253)
2017	M	73	Germany	South Africa	Safari	(254)
2017	M	53	United States of America	South Africa	Safari	(236)
2018	M	61	Netherlands	South Africa	Safari	(255)
2019	M	32	Brazil	South Africa	Safari	(243)
2021	M		Argentina	South Africa	Game hunting & Safari	(244)
2022	M	36	South Korea	Swaziland	Visit	(246)
2022	M & F	41, 45 & 54	Japan	South Africa	Leisure	(256)

in the blood (they do multiply in the endothelial cells). Due to the low sensitivity of molecular tests on blood samples for the detection of rickettsial pathogens, reliable amplification of the pathogen can only be performed in tissues at the time of autopsy (263). However, some patients may die of fulminant disease just before the development of convalescent antibodies. Thus, a substantial number of SFG rickettsioses have never been reported or have remain unnoticed, further complicating the surveillance of SFG rickettsioses. To circumvent these challenges, there is an urgent need to develop sensitive, specific, and accessible diagnostic tests. Serologic assays have some merits, but the disadvantages due to reliance on single time-point serologies limit their application.

Furthermore, PCR testing of blood offers high specificity but low sensitivity because of the low number of rickettsial organisms in the blood during acute illness with *R. rickettsii* (264). Metagenomic sequencing of blood samples offers an alternative for the broad detection of circulating pathogens; however, it remains unclear whether this approach will have sufficient sensitivity compared with nucleic acid amplification. The PCR test of skin or eschar biopsy samples is specific and sensitive, but biopsies can be difficult to obtain outside the clinical setting. In addition, diagnostic methods utilizing monoclonal antibodies that detect proteins produced by *Rickettsia*-infected cells require further investigation. If this method proves to be specific and sensitive, it could be utilized for quick testing at the point of care in the early course of illness (196). In conclusion, the current state of rickettsial diagnostics is a constraint for both surveillance and clinical efforts. Therefore, there is an urgent need for primary research focusing on rickettsial diagnostics.

Milestone in rickettsiology research in the continent and the importance of more epidemiological studies in Africa

Rickettsiology encompasses a large body of knowledge including systematics, epidemiology, genomics, molecular diagnostics, microbial interactions, immunopathology, vector biology, and transmission studies. A major focus of research in Africa has been molecular diagnostics using PCR and sequencing to amplify short DNA sequences of *Rickettsia* species in ticks and blood specimens from vertebrate hosts, including humans (46, 52, 68, 74, 165). Additionally, serology has been sparsely employed, with IFAT being the most widely used serological technique to screen serum samples for antibodies against SFG *Rickettsia* within the continent (59, 76, 265).

A major emphasis of ATBF in humans in SSA has been on foreign travelers on trips to Africa (95, 236, 240, 244, 254), with little concern for indigenous communities (76, 266). Serological data have indicated high seroprevalence in the native population

across several regions of Africa, with records registering 5–51% in western and central Africa and 16–55% in eastern and southern Africa (76, 96, 218), but few acute cases have been documented. Perhaps, this observation could be due to exposure at an early age with possible clinical cases that were ignored due to the paucity of diagnostic instrumentation at health facilities in most communities or poor visibility of inoculation eschars on pigmented skin in black Africans (88). It has also been documented that some *R. africae* variants may be more virulent than others. These variations are linked to differences in the nucleotide composition (deletion or substitution mutations) of *omp*A and *omp*B, which code for the immune-dominant surface cell antigens of *Rickettsia*, and this could affect the virulence of *R. africae* variants (185, 186). This could explain the absence of acute ATBF cases among native communities, even with a high documented seroprevalence (185). Furthermore, it has been shown in some pathogens, including *Rickettsia*, that genome reduction may lead to enhanced virulence (207). It remains to be determined if these variants of *R. africae* can be found in febrile patients within the indigenous communities.

Insufficient human resources and the required skills in molecular biology are one of the problems of science and health research in Africa. Generally, there is the problem of low numbers, uneven distribution, and immigration of experts of African origin to northern nations, including Europe and North America, for obvious reasons, including poor renumeration, weak government policies for civil servants, and incessant strikes and/or industrial disputes.

Broadly, research on vectors and VBD in Africa is gaining momentum with an increasing number of young professionals with requisite training in molecular biology and genomics, applying their knowledge and skills to comprehend pathogen-vector-host interactions, especially as it pertains to infectious diseases. Owing to the general lack of resources, it is very difficult to see a researcher/scientist with research interests that focus solely on rickettsiae or other vector-borne bacteria. In an attempt to survive in their careers, the majority of researchers are involved in surveillance for multiple pathogens across different classes. Hence, many scientists combine their research on vector-borne microorganisms (including protozoans and bacterial and viral pathogens). Nevertheless, extensive research on rickettsia has been conducted by a handful of scientists from North Africa, mostly from the Mediterranean region. This is partly supported by research collaborators from Europe cutting across Spain and France, which are part of the Mediterranean region. On the contrary, molecular surveillance has been carried out in other parts of Africa, but more focused research is needed to understand the eco-epidemiology of TBR in the continent. Specific aspects of the epidemiology that warrant further investigation include characterization of *Rickettsia* species from the blood of domestic vertebrate hosts, wild animals, and tick vectors

infesting these animals on a large scale. In addition, knowledge of the roles of small rodents and avian species in the epidemiology of rickettsial pathogens in Africa is lacking. A large-scale survey of Rickettsiae in host-seeking ticks is lacking in some parts of the continent. Other aspects include the kinetics of infection in vertebrate hosts and the vectorial capacity of common and geographically dispersed tick species to transmit rickettsial pathogens to animals and humans. Lastly, whole genome sequencing (WGS) of some of the detected rickettsial species needs to be performed to obtain high-level information on the bacteria circulating within the continent. To circumvent all these challenges, we propose that a multidisciplinary alliance of skilled experts from a broad range of individuals and institutions come together to enhance capacity and unveil additional knowledge on molecular, biological, environmental, and socioeconomic factors the common good of humanity. This alliance will help achieve the surveillance and control of rickettsiosis across the continent and further help to achieve sustainable control of rickettsiosis. Finally, there is a need for more decent animal or laboratory facilities in many parts of Africa, as only a few countries can boast a reasonable number of facilities to carry out good research.

Concluding remarks and future directions

The genus *Rickettsia* encompasses a diverse assemblage (> 30 species) of obligate intracellular coccobacilli with a unique and fascinating biology. Since the discovery of rickettsiae over a century ago, the study of their biology has been challenging, largely in part because of their intracellular nature. With several neglected but globally emerging human pathogens within this genus, it is critical to gain a better understanding of the distribution and epidemiology of these pathogens across Africa. In this review, we have highlighted broadly and in detail, the epidemiological relationship between ticks and rickettsial pathogens in Africa looking at the prevalence, distribution, and major types of rickettsial diseases in humans and animals, and reports on the detection of SFG *Rickettsia* in different tick vectors across Africa. We discussed the role of domestic animals, birds, small mammals, and wildlife in the epidemiology of SFG rickettsiae across Africa and provide insight into the problems of rickettsial diagnosis and reports in Africa. Several knowledge gaps have been identified that need to be filled, and we propose that research efforts should be directed to help solve these contributing issues.

Given the diverse ecological conditions across the African continent, it is evident that a wide range of ecosystems facilitate the development of numerous classes of arthropods, especially ticks and mammalian hosts. Therefore, we can assume that

many undescribed rickettsial species still exist in the continent, demanding improvements in surveillance for SFG *Rickettsia* across wildlife, domestic animals, avian hosts, livestock workers, agricultural workers, forest guards, veterinarians, and people living in poor rural and urban settlements in Africa. Furthermore, we advocate for the "One Health" approach to the study of rickettsial diseases in the continent.

Despite the economic importance of rickettsial disease and its potential as an emerging and re-emerging disease, little attention or recognition has been paid to it. This suggests the need to increase awareness among patients, clinicians, and scientists. In addition, there is a need to map and identify the geographical foci of various *Rickettsia* species and/or diseases, allowing the characterization of vectors and reservoirs of the disease within that particular area. To improve the epidemiological surveillance of SFG rickettsioses, among patients with febrile illness, rickettsial infections should be included as a differential diagnosis in patients with non-malarial febrile illnesses. Unlike in most parts of the world, where reasonable studies on vector competence for SFG rickettsiae have been undertaken, there is a dearth of experimental studies using field-collected tick samples in Africa to evaluate their vectorial capacity to transmit *Rickettsia* species. Therefore, we encourage more transmission experiments to be undertaken, and studies evaluating the potential of some vertebrate hosts to serve as amplifying hosts need to be conducted.

The development and use of molecular diagnostics, including PCR and sequencing, and the use of ticks as specimens, have resulted in a better understanding of the repertoire of tick-associated rickettsia. The true prevalence of SFG rickettsiae is underreported, with a resulting impact on funding and public health decisions (195). With global warming largely driven by climate changes, it is becoming apparent that the geographical range of rickettsial diseases is expanding significantly. Training physicians and/or clinicians in various parts of the world must be harmonized so that teaching on VBD includes rickettsial diseases, ensuring early emphasis on these diseases, and their inclusion as a differential diagnostic together with the current practice focused mainly on *Plasmodium*, *Leishmania*, and *Trypanosoma* parasites. In Africa, the majority of DNA-based detection and characterization of *Rickettsia* have solely been based on the use of short DNA sequences generated from Sanger sequencing following PCR amplification. Whole-genome sequence data from Africa derived from tick vectors, wildlife, and humans are scarce in public genomic repositories and/or GenBank. We advocate for more whole-genome sequence data from African isolates, particularly from tick vectors and humans. These genomic data will be used for a more in-depth core genome phylogenetic analysis, classification, and taxonomy of *Rickettsia* species within the continent.

We propose that future studies should be designed and conducted in such a way that there is comprehensive sampling

and increased genome sequencing of positive *Rickettsia* species from diverse vertebrate hosts and vectors from different ecosystems, which will help provide great insight into the evolution and diversification within this genus. Furthermore, future studies in Africa should attempt to unravel the molecular determinants responsible for the gene expression patterns observed within different vector tissues as well as the epidemiological implications of vector microbiota and rickettsial coinfections on the emergence of TBR within Africa.

Author contributions

TO perform the majority of the review of literature and initial manuscript design. TO, TS and ML were responsible for manuscript revisions, preparation and decision to publish. All authors contributed to the article and approved the submitted version.

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Conflict 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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