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*Review*

# EPIDEMIOLOGY AND DIAGNOSIS OF RICKETTSIOSES IN ANIMAL HOSTS AND TICK VECTORS

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**Summary**

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Rickettsioses are emerging and reemerging vector-borne global diseases with zoonotic importance. The aim of this review is to give an overview on the epidemiology and diagnosis of rickettsial infection in animal hosts and tick vectors. In this review, some studies found out that companion animals such as dogs, horses and camels could serve as reservoirs or carriers of the disease. The dogs are mainly infested by *Rhipicephalus sanguineus* ticks that are the main vectors of *Rickettsia conorii*, while horses and camels can be infested by other ixodid tick genera such as *Hyalomma* and *Amblyomma* which are vectors of *Rickettsia africae* beside other *Rickettsia* species in Africa including Egypt. The review also discusses the history of the disease, taxonomy, geographical distribution, prevalence, mode of infection and transmission, reservoirs or carriers, animal or tick susceptibility, pathogenesis, traditional and molecular diagnosis for rickettsiae and their tick vectors. Therefore, people dealing with animals such as farmers and veterinarians shoud be aware for the risk of exposures to ticks that may be infected with rickettsiae. Control tick programmes have to be applied from time to time to avoid any rickettsial infection to animals and humans.

**Key words**: animals, diagnosis, epidemiology, ixodid ticks, rickettsiae

## INTRODUCTION

Rickettsioses are emerging and reemerging vector-borne global diseases with zoonotic importance (Parola *et al.,* 2013). In Egypt, rickettsiae were detected in vectors, rodents, animals and human using different traditinal and advanced techniques (Soliman *et al.,* 1989; Corwin *et al.,* 1992; Lange *et al.,* 1992; Reynolds, 2004; Loftis *et al.,* 2006a,b; Socolovschi *et al.,* 2010; Abdel-Shafy *et al.,* 2012; Abdullah *et al.,* 2016). The genus *Rickettsia* includes obligatory intracellular short Gram-negative bacillary bacteria. These microorganisms retain basic fuchsin when stained by Gimenez (Gimenez, 1964; Kang *et al.,* 2014). The genus

*Rickettsia* is classified into spotted fever group (SFG) rickettsiae, typhus group (TG) rickettsiae, *Rickettsia belli* group and *Rickettsia candensis* group (Merhej & Raoult, 2011). Rickettsiae particularly SFG are mainly transmitted through transstadial and transovarial routes by ticks (Raoult & Roux, 1997). Rickettsiae associated with ixodid (hard) ticks transmit the microorganisms to vertebrates through tick bites via their salivary secretions, or through faeces and blood transfusion (Socolovschi *et al.,* 2009b).

In general, rickettsioses have low mortality but with high morbidity except some *Rickettsia* spp. which are characterised with high mortality in dogs and people as *R. rickettsii*. Four to ten days after tick bitting, the clinical signs of rickettsioses appear. The typical symptoms are headache, fever, rash, muscle pain, local lymphadenopathy. A characteristic eschar (tache noire) takes place at the site of tick bite. The clinical signs of rickettsioses may differ from one rickettsial species to another. Common non-specific clinicopathological abnormalities due to rickettsioses include mild leukopaenia, anaemia, and thrombocytopenia. Furthermore, hepatic, renal abnormalities, hyponatremia and hypoalbuminemia may occur (Raoult & Roux, 1997; Parola *et al.,* 2005; 2013).

Recently, the diagnosis of rickettsial infection depends on molecular tools that have facilitated the identification of new and previously recognised rickettsiae (Parola *et al.,* 2013). The two major genes in SFG rickettsiae are *gltA* (citrate synthase) and *OmpA* (outer membrane protein A) (Roux *et al.,* 1996; 1997, Fournier *et al.,* 1998a; Mediannikov *et al.,* 2004). These two genes have high variability between species of SFG rickettsiae (Roux *et al.,* 1996; Guillemi *et al.,* 2015).

An accurate identification of tick species is important to control any disease transmitted by ticks. Traditionally, taxonomical keys of tick species mainly depend on the morphological description of male and female adults by light microscope or scanning electron microscope. It is difficult to discriminate tick specimens by traditional techniques when they are fully engorged, physically damaged, in immature stages (Caporale *et al.,* 1995; Guglielmone *et al.,* 2006) and at subspecies or at one group (Dantas-Torres *et al.,* 2013; Gray *et al.,* 2013). Recently, the molecular identification of ticks by DNA markers is essential. The DNA markers include nuclear (18S ribosomal RNA), mitochondrial (cytochrome oxidase subunit-1, 12S ribosomal RNA and 16S ribosomal RNA) genes and nuclear regulatory non-translated stretches (ribosomal internal transcribed spacer 2) (Chen *et al.,* 2012; Nava *et al.,* 2012; Lui *et al.,* 2013; Lv *et al.,* 2014a,b).

The aim of this review is to give an overview on the epidemiology and diagnosis of rickettsial infection especially in animal hosts and tick vectors. This review discusses some topics related to rickettsioses as history of the disease, taxonomy, geographical distribution, prevalence, reservoirs or carriers, tick or animal susceptibility, traditional diagnosis by stain and molecular diagnosis in animal hosts and tick vectors. Furthermore, the molecular identification of tick vectors was spotlighted in this review.

## HISTORY OF RICKETTSIOSES

In 1899, tick-borne rickettsiosis was firstly described clinically as Rocky Mountain spotted fever (RMSF) by Maxey (1899). King (1906) and Ricketts (1906; 1909) reported that the wood tick

*Dermacentor* has a role in the transmission of the causative agent of RMSF. Ricketts also demonstrated that the causative agent of RMSF can be transmitted from infected ticks to their progeny transovarially and that the organism can be isolated in guinea pigs. Moreover, Ricketts died of typhus and RMSF and the causative agent was subsequently named *Rickettsia rickettsii* (Ricketts, 1906; 1909). In 1933, dogs were reported to be susceptible to infection with *R. rickettsii* by Badger (1933). Also, Keenan *et al.* (1977a,b) induced experimentally infection in dogs with *R. rickettsii*. The first evidence of naturally occurring RMSF in dogs was reported by Lissman & Benach (1980).

In Tunisia, Conor & Bruch (1910) reported the first case of Mediterranean spotted fever (MSF). Thereafter, the disease was known as Boutonneuse Fever. In 1925, Marseille, the typical inoculation eschar was described at tick bite site (Olmer, 1925). Brumpt (1932) demonstrated the role of *Rh. sanguineus* tick in transmission of *Rickettsia conorii* (the causative agent of MSF).

For many decades, the rickettsiologists believed that the sole rickettsial agents were associated with specific sites (Raoult & Roux, 1997). In America, *R. rickettsii* was believed to b the only agent of SFG. In the same line, *R. conorii*, *Rickettsia sibirica*, *Rickettsia australis* was reported in Europe, (Africa or China) and Australia, respectively.

Until the 1990s, *R. conorii* was considered the only rickettsial agent in Africa (Raoult & Roux, 1997). In 1990, *Rickettsia africae* was isolated from the tick *Amblyomma hebraeum* in Zimbabwe by micro-immunofluorescence typing (Kelly & Mason, 1990; Kelly, 2001). Kelly and colleagues isolated *R. africae* by shell vial cell culture and named the disease African tick-bite fever (ATBF), as a newly recognised *Rickettsia* (Kelly *et al.,* 1991). In Southern Africa, *A. hebraeum* was considered a vector of *R. africa*e (Kelly *et al.,* 1996). Furthermore, *R. conorii* and *R. africae*, seven additional species of SFG rickettsiae were reported to be rickettsial pathogens in Africa (Letaief, 2006; Cazorla *et al.,* 2008).

Another *Rickettsia* species were reported and isolated in Africa as *Rickettsia aeschlimannii*. In Morocco during the year 1992, *R. aeschlimannii* was firstly isolated from *Hyalomma marginatum* and in 1997 it was considered a new SFG *Rickettsia* (Beati *et al.,* 1997). *Hyalomma* sp. were reported to be vectors and reservoir of *R. aeschlimannii* (Matsumoto *et al.,* 2004). Moreover, the novel rickettsial agent, *R. massiliae* was isolated from *Rh. sanguineus* collected near Marseille, France (Beati & Raoult, 1993). In North Africa, *R. massiliae* was found in *Rh. sanguineus* and *Rh. bursa* ticks collected from Morocco (Sarih *et al.,* 2008; Boudebouch *et al.,* 2009). This rickettsial species was also detected in *Rh. turanicus* and *Rh. sanguineus* ticks collected from Algeria (Bitam *et al.,* 2006) and in *Rh. sanguineus* collected from Tunisia (Khrouf *et al.,* 2014).

In Egypt, tick-borne rickettsial agents were reported serologically in animals and people (Botros *et al.,* 1989; Soliman *et al.,* 1989; Corwin *et al.,* 1992; 1993; Reynolds, 2004). SFG of *Rickettsia* species were detected in *Hyalomma* species and *Rh*. *sanguineus* collected from Sinai using immunostaining method and PCR (Lange *et al.,* 1992; Loftis *et al.,* 2006a,b). Socolovschi *et al.* (2010) reported *R. siberica mongolitimonae* in a traveller from Egypt returned to France. Moreover, *R. africae* was reported for the first time in

Egypt by Abdel-Shafy *et al.* (2012). *R. aeschlimannii* was reported by the same authors in *Hyalomma* spp.

## ETIOLOGY AND TAXONOMY

The genus *Rickettsia* comprises obligatory intracellular short rods, cocci or thread-like Gram-negative bacillary bacteria. These microorganisms retained basic fuchsin when stained by Gimenez (Gimenez, 1964; Kang *et al.,* 2014). This hemolymph staining technique was described in the mid 1950s (Gimenez, 1964).

An extensive reorganisation was performed on the taxonomy of rickettsiae (Raoult & Roux, 1997; Hechemy *et al.,* 2003). The order Rickettsiales is divided into two families – Anaplasmataceae and Rickettsiaceae. The sequences of five genes (*gltA*, *ompA*, 16S rRNA, *ompB*, and *sac 4* or *gene D*) are recently used in classification of rickettsiae at the level of species, group and subspecies (Dumler *et al.,* 2001; Fournier *et al.,* 2003). The genus *Rickettsia* is divided into four groups; typhus (TG), spotted fever (SFG), *Rickettsia belli* and *Rickettsia candensis* (Fournier & Raoult, 2007; Merhej & Raoult, 2011). Moreover, Fournier and his colleagues mentioned that the most variable sequences at the level of rickettsial species or strain were intergenic spacers (Fournier *et al.,* 2004).

The SFG rickettsiae contain several pathogenic microorganisms which cause tick-borne rickettsioses in animals and humans. They include seventeen *Rickettsia* species: 1) *R. rickettsii* (Rocky Mountain spotted fever, RMSF), 2) *R. conorii conorii* (Mediterranean spotted fever, MSF), 3) *R. conorii israelensis* (Israeli spotted fever, ISF), 4) *R. conorii caspia* (Astrakhan spotted fever), 5) *R. conorii indica* (Indian tick typhus rickettsiosis), 6) *R. africae* (African tick-bite fever, ATBF), 7) *R. heilongjiangensis* (Far-eastern tick borne rickettsiosis), 8) *R. australis* (Queensland tick typhus), 9) *R. slovaca* (Tick-borne lymphadenopathy and *Dermacentor*-borne necrosis erythema lymphadenopathy, TIBOLA/DEBONEL), 10) *R. sibirica sibirica* (North Asian tick typhus or Siberian tick typhus), 11) *R. sibirica mongolitimonae* (Lymphangitis associated rickettsiosis), 12) *R. honei* (Flinders Island spotted fever), 13) *R. japonica* (Japanese or Oriental spotted fever), 14) *R. parkeri,* 15) *R. aeschlimannii,* 16) *R. massiliae* and 17) *R. raoultii* (Parola *et al.,* 2005). There are numerous symbiont rickettsiae associated with ticks; their pathogenicity is still unknown (Parola & Raoult, 2001).

## EPIDEMIOLOGY OF RICKETTSIOSES

In general, the epidemiology of arthropod-borne diseases is affected by the disease triangle that includes three main factors: pathogen, host (vector, animal and human) and environment (Harrus & Baneth, 2005).

### *Geographical distribution*

In general, rickettsioses are global emerging and reemerging vector-borne infectious diseases (Parola *et al.,* 2005; 2013). Moreover, SFG rickettsioses are geographic disease because each tick species prefers specific optimal environmental conditions, biotopes and hosts (Parola & Raoult, 2001). Therefore, the distribution of ticks is restricted to a particular area that is considered risk area for the disease (Parola *et al.,* 2005). Letaief (2006) affirms that the geographical distribution of rickettsiae is determined by the incidence of their arthropod hosts. The seasonal

incidence of rickettsioses is parallel to the tick activity.

For example, MSF caused by *R. conorii* is endemic in Mediterranean areas. *Rhipicephalus sanguineus,* the main vector of *R. conorii*, could survive in warm climates and even cooler regions. It attacks dog kennels and humans that live in these climates. However, *R. conorii* had not been described in USA (Parola *et al.,* 2005).

Various tick vectors were previously considered to be restricted to a particular geographical area. Recently, many SFG rickettsiae were recognised and detected on different continents (Parola *et al.,* 2013). For example, *R. africae* was SFG restricted in central and southern Africa and its vector was *Amblyomma* spp. (Kelly *et al.,* 1996; Macaluso *et al.,* 2003; Socolovschi *et al.,* 2007), but it was recently isolated from *Hyalomma* spp. in Egypt (Abdel-Shafy *et al.,* 2012; Abdullah *et al.,* 2016). In Brazil, Silva *et al.* (2018) recorded *Rickettsia amblyommatis* in the tick *Amblyomma pseudoconcolor*. In Panama, Martínez-Caballero *et al.* (2018) firstly detected *R. rickettsii* in *Rh. sanguineus*. In South America, three rickettsial strains, Atlantic rainforest, NOD, and Parvitarsum were isolated from *Amblyomma ovale*, *Amblyomma nodosum*, and *Amblyomma parvitarsum* ticks, respectively. These three strains are phylogenetically closely related to *Rickettsia parkeri*, *R. africae*, and *R. sibirica* (Nieri-Bastos *et al.*, 2018). In Bulgaria, Nader *et al*. (2018) detected by sequencing the presence of *Rickettsia monacensis, R. helvetica,* and *R. aeschlimannii* in ticks belong to the genera *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes* and *Rhipicephalus*. Furthermore, rickettsiae was determined in either animal hosts or tick vectors in many countries such as Malta (Torpiano & Pace, 2018), Argentina (Saracho-Bottero *et al*., 2018), Nigeria (Kamani *et al*., 2018), China (Han *et al*., 2018), Mongolia (von Fricken *et al*., 2018), Cameroon (Vanegas *et al*., 2018), Lebanon (Fernández de Mera *et al*., 2018), USA (Eremeeva *et al*., 2018), Russia (Igolkina *et al*., 2018) and Poland (Stańczak *et al*., 2018).

*Prevalence of rickettsioses*

In general, rickettsioses are characterised by high morbidity and low mortality rates except some *Rickettsia* spp. which induced high mortality in dogs and people as *R. rickettsii* in Brazil (Brazilian spotted fever) with challenging diagnosis due to its non-specific signs (Walker, 2002; Labruna *et al.,* 2009). However, MSF had a global death rate of 3.6 % (Kernif *et al.,* 2012b). Fatality rates in dogs infected with rickettsiae in the USA were reported to be 3% (Greene, 1987) and 7% (Greene *et al.,* 1985) while the incidence rate of ATBF was 1.9% in Norway and 25% in the Equator but may reach 74% of travellers' cases in South Africa when occurring in clusters (Fournier *et al.,* 1998b; Caruso *et al.,* 2002; Jensenius *et al.,* 2003).

Currently, limited information is available on the prevalence of rickettsioses in animal hosts. Dogs have been considered sentinels and sometimes horses were found in dog habitats (Campos *et al.,* 2016). However, seroprevalence of *Rickettsia* spp. in dogs and horses in endemic region such as Juiz de Fora and Minas Gerais in Brazil was high; up to 68–81% (Vianna *et al.,* 2008; Pacheco *et al.,* 2011), while in non-endemic area in Brazil, the seroprevalence was less than 15% (Sangioni *et al.,* 2005; Cunha *et al.,* 2014; Silveira *et al.,* 2015). In camels, Kamani *et al*. (2015) detected 18.8% *Rickettsia* spp. in camel blood samples

from Nigeria, Mentaberre *et al.* (2013) reported 83% *Rickettsia* spp. in camels by ELISA in Spain and Wernery *et al.* (2001) detected the rickettsiae in stained blood films in Dubai, UAE. In Lithuania, Mardosaitė-Busaitienė *et al.* (2018) stated that the prevalence of *Rickettsia* spp. in small mammals was 27.6%. In Germany, the prevalence of *Rickettsia* in rodents was determined by real-time PCR targeting *gltA*, *ompB* and *ompAIV* genes (Fischer *et al*. 2018). They found *Rickettsia helvetica* (90.9%), *Rickettsia felis* (7.8%) and *Rickettsia raoultii* (1.3%).

In ticks, the transstadial and transovarian system transmitted rickettsiae to vertebrate hosts during blood meal, which maintained bacteria in nature and made ticks simultaneously vectors and reservoirs (Raoult & Roux, 1997; Parola *et al.,* 2005). Under field conditions, the rickettsial infection incidence tends to be lower than 1% because the rickettsiae can kill ticks (Niebylski *et al.,* 1999; Levin *et al.,* 2009; Socolovschi *et al.,* 2009a). Therefore, the infection rate of *Rickettsia* spp. in *Rh. sanguineus* was reported to be 1.3–2.9 % (Demma *et al.,* 2005; Moraes-Filho *et al.,* 2009). So, it is thought that vertebrates play a more dominant role as a reservoir and persistence of rickettsiae than ticks. In Brazil, Silva *et al.* (2018) found that 90.9% of the ticks *Amblyomma pseudoconcolor* collected from *Euphractus sexcinctus* were positive for infection with *Rickettsia amblyommatis*. In Bulgaria, the high prevalence of *Rickettsia* spp. (48.3%) was detected by using quantitative real-time PCR in ticks collected by flagging method (Nader *et al*., 2018). In Romania, Andersson *et al*. (2018) detected *Rickettsia helvetica*, *R. raoultii*, *R. massiliae*, *R. monacensis*, *R. slovaca* and *R. aeschlimannii* in the ticks collected from domestic and wild animals. They found that the prevalence of rickettsial infection was 10.6% (87/824) of ticks.

*Mode of infection and transmission*

Rickettsioses are transmitted to vertebrate hosts by bite of infected ticks through salivary secretions and blood transfusion (Raoult & Roux, 1997). The salivary glands of ticks facilitate the feeding of ticks and act as vehicles, and propagation sites for rickettsiae (Santos *et al.,* 2002; Socolovschi *et al.,* 2009a). However, the infection by tick faeces is unknown. The faeces transmission proves the low infection of *R. rickettsii* in guinea pigs (Philip, 1959; Rehacek, 1965).

Hard ticks acquire rickettsiae through different sources. The initial tick infection with rickettsiae occurs by feeding of non-infected ticks on rickettsaemic hosts. Sufficient blood levels of rickettsiae in vertebrate hosts are required for infection (Rehacek, 1989). Also, ticks become infected with rickettsiae through transovarial transmission (Parola & Raoult, 2001; Anderson & Magnorelli, 2008; Socolovschi *et al.,* 2009b). The other transmission route is the transstadial transmission in which rickettsiae transfer from stage to stage (Parola & Raoult, 2001). Sexual transmission is reported for acquiring rickettsiae by infected male ticks to non-infected females (Schriefer & Azad, 1994). In addition, cofeeding method in which several ticks feed at closely situated bite sites in reported, which leads to direct rickettsiae transmission from infected to uninfected ticks (Philip, 1950).

*Reservoirs and carriers*

SFG rickettsiae circulate between wild vertebrates and arthropods vectors (Telford & Parola, 2007). As early as 1967, Burgdorfer and Varma stated that the most Ixodidae infected with SFG

rickettsiae were considered vectors and reservoirs. This attributes to the transstadial and trasovarial transmission of rickettsiae (Burgdorfer & Varma, 1967; Parola *et al.,* 2005).

Dogs play an important role in maintaining rickettsial infection in the nature. In this way, the dogs obtain *R. conorii* infection from infected *Rh. sanguineus* and transmit rickettsiae to another uninfected tick (Levin *et al.,* 2012). That is the first evidence that dogs can act as reservoir for rickettsiae (Piranda *et al.,* 2011). Other authors suggested that capybaras and opossums as well as wild mammals and birds play an important role in amplifying and keeping of rickettsiae in nature (Horta *et al.,* 2004; Souza *et al.,* 2009; Keysary *et al.,* 2011; Socolovschi *et al.,* 2011; Movila *et al.,* 2012; Ionita *et al.,* 2016). Other studies suggested some other potential animal reservoirs of *Rickettsia* spp.; cattle and camels for *R. africae* (Reye *et al.,* 2012), wild boars and domestic ruminants for *R. slovaca* (Ortuno *et al.,* 2007; 2012) and sika deer for *R. helvetica* (Inokuma *et al.,* 2008); however, additional studies are required to confirm animal reservoirs.

*Animal susceptibility*

Dogs and horses are important animals that have a role in the epidemiology of SFG rickettsioses. They act as keepers and amplifier hosts for rickettsiae due to their contacts to vegetations, ticks and other elements of the nature. Horses cover great areas and are able to spread the ticks infected with rickettsiae (Lemos *et al.,* 1996; Sangioni *et al.,* 2005; Freitas, 2007). Meanwhile, dogs are bringing infested ticks from outside to indoors and can transmit the rickettsial infection to humans (Mcdade & Newhouse, 1986).

Dogs can serve as a readily available source of nutrition for many blood-feeding arthropods and are frequently exposed to tick infestation (Otranto *et al.,* 2010). They serve as indicator and epidemiological marker for the presence of vector-borne diseases such as rickettsioses (Tesouro *et al.,* 1998; Ortuno *et al.,* 2009). Dogs are human companions, extensively exposed to tick infestation, so they play a role as sentinels in an epidemiological approach of rickettsioses (Campos *et al.,* 2016). Some cases of *R. rickettsii* were reported in dogs and their human owners in the USA (Paddock *et al.,* 2002; Elchos & Goddard, 2003; Kidd *et al.,* 2006) as well as in Brazil (Pinter *et al.,* 2008; Piranda *et al.,* 2011). Also, dogs are considered to be the sentinels of *R. conorii* infection (Parola *et al.,* 2005; Ortuno *et al.,* 2009).

Regarding the sex of animals, no sex predilection has been observed by Greene *et al.* (1985) and Gasser *et al.* (2001), while other reports demonstrated that males were more susceptible to *R. conorii* infection than females (Solano-Gallego *et al.,* 2006a; 2008). Both male dogs and men are at risk for more severe illness with *R. rickettsii* and *R. conorii* (Parola *et al.,* 2005, Greene & Breitschwerdt, 2006).

Moreover, Solano-Gallego *et al.* (2006b) recorded a significant difference between *R. conorii* infection rates in two dog breed groups, Yorkshire terrier and mixed breed. In contrast, no significant difference was reported in *R. rickettsii* positive samples from Yorkshire terrier dogs. However, the purebred dogs were more susceptible to *R. rickettsii* infection (Greene & Breitschwerdt, 2006).

Higher seroprevalence was reported in dogs highly exposed to *Rh. sanguineus* than in dogs living as pets or in kennels and subjected to tick control programmes

(Ortuno *et al.,* 2009). Greene *et al.* (1985) found a predilection for dogs less than 2 years of age with respect to infection with *R. rickettsii*, whereas in another study, 93% of dogs infected with RMSF were older than 2 years (Gasser *et al.,* 2001). Moreover, Cunha *et al.* (2014) observed that older animals were more reactive than younger animals, which may be attributed to the prolonged repeated exposure to ticks of older animals or low immunity. Therefore, there was a significant difference among age groups.

The participation of horses as reservoir of infection is arguable. Some literature sources reported high prevalence of rickettsiae in both horses and dogs (Lemos *et al.,* 1996; Horta *et al.,* 2004; Sangioni *et al.,* 2005; Pinter *et al.,* 2008) while Cunha *et al.* (2014) stated that horses were bad references for circulation of rickettsiae. Moreover, Sangioni *et al.* (2005) and Riveros-Pinilla *et al.* (2015) suggested that the presence of antibodies in horses is a decent marker of the spread of *R. rickettsii* in zones.

Riveros-Pinilla *et al.* (2015) reported the absence of statistical significant association between infection rate with *Rickettsia* spp. in horses and age, sex and breed, in line with Andersson (2013) who suggested that age, sex and breed in horses were not considered risk factors.

In camels, rickettsioses were reported in blood film staining by Wernery *et al.* (2001), while Wernery & Kaaden (2002) mentioned that the disease had not been reported in old world camels and these animal hosts had no role in the cycle of rickettsiae. However, some data reported the presence of SFG rickettsae in some species of the genus *Hyalomma* collected from camels (Abdel-Shafy *et al.,* 2012; Demoncheaux *et al.,* 2012; Kernif *et al.,* 2012a; Abdullah, 2017). Moreover, rickettsiae were detected in camels by ELISA (Mentaberre *et al.,* 2013) and by PCR in Nigeria (Kamani *et al.,* 2015). In general, camels come in contact with other animals at the livestock markets. This facilitates the transfer of ticks from one animal to another. On the other hand, *Hyalomma* spp. are able to attack humans (Mediannikov *et al.,* 2010). This ability facilitates the transmission of *Rickettsia* spp. to humans who deal with camels.

Humans are only accidental or occasional hosts and rarely involved in subsequent transmission of rickettsiae, so they must be considered an end host that has no role in the maintenance of rickettsiae (Socolovschi *et al.,* 2009b). Several reports stated the RMSF in humans with dog companions (Paddock *et al.,* 2002; Elchos & Goddard, 2003).

*Tick susceptibility*

*Rickettsia rickettsii* is transmitted by several tick genera as *Dermacentor* spp. (King, 1906; Ricketts, 1906; 1909), and other ticks as *Haemaphysalis leporispalustris*, *Amblyomma americanum*, *Ixodes dentatus* and *Rh. sanguineus* (Parker *et al.,* 1943; 1952). *Rickettsia conorii* was associated with one tick vector, *Rh. sanguineus* (Brumpt, 1932). Moreover, *R. africae* in South Africa was associated only with *Amblyomma* spp. (Parola & Raoult 2001; Parola *et al.,* 2005), but now *Hyalomma* spp. can transmit *R. africae* in North Africa (Abdel-Shafy *et al.,* 2012; Kernif *et al.,* 2012a; Kleinerman *et al.,* 2013; Abdullah, 2017). Also, Ogo *et al.* (2012) reported *R. africae* in *Rh. sanguineus*.

Lalzar *et al.* (2012) reported that the seasonal changes could influence the facultative relationship between *Rickettsia* and its tick vector. Moreover, the densities

of rickettsiae were equal through male and female ticks.

*Molecular identification of tick vectors*

Some morphological features are similar at both intra-species and inter-species level. This similarity limits the accuracy of morphological taxonomic key especially in *Rh. sanguineus* group (Walker *et al.,* 2000; Guglielmone *et al.,* 2014; Nava *et al.,* 2015). However, molecular tools provide an accurate characteristics at the level of species and subspecies confirming morphological identification. Historically, the phylogeny of hard ticks using 12S rDNA sequences and morphological characters were studied by Beati & Keirans (2001). They concluded that the genus *Boophilus* was monophyletic and arose within the genus *Rhipicephalus*. Other studies agreed with this conclusion but using the sequences of CO 1, ITS 2 and 18S rRNA besides 12S rRNA (Murrell *et al.,* 2001; Barker & Murrell, 2003; Murrell & Barker, 2003). In Egypt, the sequence and phylogenetic analyses of five DNA markers (18S rDNA, ITS2, 12S rDNA, CO1 and 16S rDNA) were established for molecular taxonomy of *Rh. sanguineus* and *H. dromedarii* (Abdullah *et al.,* 2016). They confirmed the suitability of the mitochondrial genes (12S rDNA, CO1 and 16S rDNA) for more accurate identification of tick species than the nuclear ones (18S rDNA and ITS2).

Over the last decade, many studies confirmed the suitability of DNA markers for rapid and reliable species identification of ticks (Latrofa *et al.,* 2013). These molecular markers included nuclear i.e.18S rRNA, mitochondrial i.e. 12S, 16S rRNA, and CO1 genes and nuclear regulatory non-translated stretches i.e. ITS2 (Chen *et al.,* 2012; Nava *et al.,* 2012; Lui *et al.,* 2013; Lv *et al.,* 2014a,b). The 18S rRNA was used for taxonomy at generic level (Dobson & Barker, 1999; Mans *et al.,* 2011) whereas 16S rRNA, CO1, and ITS2 were the best markers at the tick species level (Mangold *et al.,* 1998; Norris *et al.,* 1999; Guglielmone *et al.,* 2006; Lynn & Strüder-kypke, 2006; Chitimia *et al.,* 2010; Song *et al.,* 2011; Chen *et al.,* 2012; Nava *et al.,* 2012; Lui *et al.,* 2013; Lv *et al.,* 2014a,b). Furthermore, 12S rRNA was found suitable in determining the relationships between diverged branches in recent phylogenies of the tick taxonomy (Norris *et al.,* 1999; Beati & Keirans, 2001; Lv *et al.,* 2014b).

Several studies were applied for tick species identification using mitochondrial and nuclear markers which reported that the mitochondrial genome had strict maternal inheritance (Navajas & Fenton, 2000; Erster *et al.,* 2013). On the other hand, a single pair of mitochondrial primers produced small-size PCR products from different species with fast evolution than nuclear ones (Shao & Barker, 2007). Moreover, the reference mitochondrial database is more available than nuclear marker and facilitates comparing the new sequences obtained from tick samples with that recorded before due to increased number of mitochondrial genes and genomes of different tick species (Beati & Keirans, 2001; Dergousoff & Chilton, 2007; Shao & Barker, 2007; Chitimia *et al.,* 2010; Song *et al.,* 2011).

## PATHOGENESIS OF RICKETTSIOSES

Pathogenic SFG rickettsiae invaded animal hosts and humans through the bite of infected ticks into the endothelial cells of blood vessels (Raoult & Roux, 1997). Pathogenesis of rickettsiae was variable among different species according to the expression of particular rickettsial genes

(Parola *et al.,* 2005). The *OmpA* gene in *R. rickettsii* helps the adhesion and entry of rickettsiae inside the endothelial cells (Li & Walker, 1998). Also, the *OmpB* played the same role in *R. japonica* (Uchiyama, 2003).

After internalisation and phagocytosis, rickettsiae lyse the phagosomal membrane to propagate in the cytoplasm and nucleus. Rickettsiae move between cells by actin mobilisation (Walker *et al.,* 2003). The target cells of rickettsiae are endothelial cells and they spread in all organs including brain and lungs (Walker *et al.,* 2003). Rickettsial pathogens are harboured in internal organs and tissues especially bone marrow, which is opposed to the infiltration of antibodies and antibiotics. Therefore, the persistence of rickettsiae in bone marrow may lead to relapse even with a prolonged treatment (Stiles, 2000; Levin *et al.,* 2014).

Rickettsiae replicate in the vascular endothelium causing vasculitis, resulting in platelets and coagulation system activation, thrombosis, increased vascular permeability. Moreover, cytopathic effects and cellular activity of *Rickettsia* endotoxins triggered haemostatic disorders as thrombocytopaenia and prolonged clotting time (Davidson *et al.,* 1990).

The pathogenesis of *R. rickettsii* in dogs includes a combination of three mechanisms. The first is endothelial cell response to injury leading to promotion of a proinflammatory and thrombotic state. Second, microvascular thrombosis and endothelial injury cause oxidative stress with subsequent cell death. Finally, platelet homeostasis is further affected by immune-mediated platelet destruction (Silverman & Santucci, 1988; Eremeeva & Silverman, 1998).

Animal models (as guinea pigs) have been used to predict the pathogenicity of various rickettsiae but this technique turned out to be unreliable with them as some highly pathogenic strains of *Rickettsia* spp. produced only mild illness in guinea pigs. However, the determination of pathogenic role of tick-borne rickettsiae was dependent on isolation and detection of organism from host with signs of disease (Parola *et al.,* 2005).

## DIAGNOSIS OF RICKETTSIOSES

The diagnosis of rickettsial infections is often difficult. In early stage of infection, the symptoms resemble several infectious diseases. A history of exposure to the tick vector is helpful but cannot be relied upon (Kernif *et al.,* 2012b).

### *Clinical signs, haematological and biochemical changes*

Dogs were reported to be infected with *R. conorii* (Estrada-Pena & Venzal Bianch, 2006; Solano-Gallego *et al.,* 2006b; Levin *et al.,* 2012) and *R. rickettsii* (Breitschwerdt *et al.,* 1988; Gasser *et al.,* 2001; Labruna *et al.,* 2009). Only pain, erythema and oedema were observed in dogs experimentally infected with *R. conorii* (Kelly *et al.,* 1992). Solano-Gallego *et al.* (2006b) observed febrile illness in dogs infected with *R. conorii* while other reports stated that no statistically significant differences existed between sick and clinically healthy dogs (Solano-Gallego *et al.,* 2006b; Ortuno *et al.,* 2009).

Canine rickettsioses caused by *R. conorii* were characterised by sub-clinical infection and less commonly acute diseases (Kelly *et al.,* 1992). Acute clinical disease was observed in dogs infected with *R. rickettsii* (Solano-Gallego *et al.,* 2006a, 2008). Therefore, the clinical signs observed in dogs experimentally infected

with *R. rickettsii* included fever, lethargy, anorexia, bilateral ocular discharge, sclera congestion, conjunctival oedema, ocular and oral petechiae and tremors. Moreover, haematological and biochemical changes were in the form of thrombocytopaenia, leukocytosis and anaemia (Piranda *et al.,* 2008; 2011; Levin *et al.,* 2014). In the advanced stage of *R. rickettsii* infection, dogs suffered from oedema in the extremities that may involve the lips, ears, penile sheath and scrotum (Greene & Breitschwerdt, 2006).

In canine RMSF, ocular manifestations are considered useful diagnostic signs (Davidson *et al.,* 1989). They reported that the ocular findings included bilateral conjunctival vascular injection, multifocal retinal haemorrhages, anterior uveitis and petechial haemorrhages in the iris stroma, whereas ocular haemorrhages were the most common ophthalmic sign of RMSF (Stiles, 2000). However, the most common cutaneous lesions in RMSF were oedema as well as petechial and ecchymotic haemorrhages and severe dermal necrosis in region in which oedema and haemorrhage were severe such as scrotum pinnae and limbs (Weiser & Greene, 1989).

In a retrospective study on 30 dogs with RMSF, Gasser *et al.,* (2001) reported that the most common clinical signs were lethargy, anorexia, fever, vomiting, diarrhoea, ocular abnormalities, weight loss, lymph adenomegaly, oedema and ocular signs (sclera injection and retinal vasculitis), and less common clinical signs comprised arthropathic, cutaneous necrosis, petechiae, ecchymosis, myalgia and neurologic dysfunction including ataxia, hyperesthesia, vestibular signs and seizures (Low & Holm, 2005). In the same study Gasser *et al.* (2001) found that 85% of dogs infected with RMSF were thrombocytopaenic and manifested other laboratory abnormalities as leukopaenia early in the course of disease followed by progressive leukocytosis, increased liver enzymes, coagulation abnormalities, anaemia, hypoalbuminaemia, hypercholesterolaemia, hyponatraemia and lymphocytic pleocytosis in cerebrospinal fluid. Moreover, Levin *et al.,* (2014) reported that RMSF infected dogs develop pronounced monocytosis and granulocytosis after five days from experimental inoculation. Meanwhile, Scorpio *et al.* (2008) stated that there were no specific haematological or biochemical differences between seronegative and seropositive dogs with respect to rickettsiae.

SFG rickettsioses were found to be fatal in some infected dogs and their owners as reported by Elchos & Goddard (2003). They reported two dogs suffering from seizure, petechiae of the gums and sclera, inability to stand, pale mucous membranes, fever and mild oedema of the face and forelimbs. In addition, laboratory abnormalities included leukocytosis, severe thrombocytopaenia, hyponatraemia, hypocalcaemia, bilirubinaemia and hypoalbuminaemia, subsequently dogs died due to improper diagnosis and treatment.

In horses, no clinical signs were observed even with high titres of *R. rickettsii* and other rickettsiae and the clinical manifestation of the disease in horses is rare (Lemos *et al.,* 1996; Medeiros *et al.,* 2013). Riveros-Pinilla *et al.,* (2015) detected antibodies against *Rickettsia* spp. in apparently healthy horses.

Few data are available on SFG rickettsioses in camels and their clinical signs. Rickettsiae were detected serologically in camels by Mentaberre *et al.* (2013) and detected in stained blood film by Wernery *et al.* (2001). The latter authors reported some clinical features of

rickettsiosis in camels as depression, lethargy, emaciation and recumbency and enlarged oedematous lymph nodes (Wernery *et al.,* 2001).

In general, many studies demonstrated the clinical signs of SFG rickettsioses in humans. The clinical symptoms began 4 to 10 days after tick bitting and included fever, headache, muscle pain, rash, local lymphadenopathy and a characteristic inoculation eschar (tache noire) at the site of tick bite (Raoult & Roux, 1997; Watt & Parola, 2003; Parola *et al.,* 2013). Common non-specific disorders associated with rickettsial infection included mild leukopaenia, anaemia and thrombocytopaenia, in addition to hepatic and renal disorders, hyponatraemia and hypoalbuminaemia (Raoult & Roux, 1997; Parola *et al.,* 2005; 2013).

*Blood film and hemolymph staining technique*

In the blood of infected animal hosts, *Rickettsia* spp. circulated in low numbers even in the acute phase (Breitschwerdt *et al.,* 1990; Parola, 2005). Blood film stained with a specific rickettsial stain (Gimenez stain) showed red cocci, rods or thread-like rickettsiae inside blood cells, as rickettsiae are compulsory intracellular short Gram-negative bacillary bacteria that held basic fuchsin (Gimenez, 1964). In ixodid ticks, rickettsiae circulated in the haemolymph of infected ticks (Santos *et al.,* 2002). However, haemolymph staining technique by Gimenez was applied on haemolymph of ticks, keeping ticks undamaged for further identification and rickettsial isolation (Gimenez, 1964; Burgdorfer, 1970).

*Molecular diagnosis of rickettsiae in animal hosts*

The diagnosis of rickettsioses is a challenge because of non-specific clinical signs and laboratory abnormalities or subclinical infection (Gasser *et al.,* 2001; Parola *et al.,* 2005; 2013). Serological methods – microimmunofluorescence (MIF) and western blotting (WB) – were frequently used for diagnosis of SFG rickettsioses, but there are drawbacks of serological methods such as negative serological titres, antigenic cross-reactions among SFG rickettsiae (Breitschwerdt *et al.,* 1990; Parola *et al.,* 2005) Therefore, serological diagnosis of rickettsioses is adequate but insufficient for accurate identification of the causative agent (Parola *et al.,* 2005; 2013). In addition, cell culture can detect, isolate and describe new species of rickettsiae but it is still difficult to be performed and few reference labs can apply it (Parola *et al.,* 2005).

To avoid delay in diagnosis of rickettsioses, molecular techniques (including PCR and sequencing) were applied to allow more accurate and rapid detection and identification of rickettsiae with improved sensitivity and specificity of the diagnosis (Parola *et al.,* 2013; Guillemi *et al.,* 2015). Primers were used in amplifying sequences of several genes including *OmpA*, *OmpB*, *gltA* and gene D (Roux *et al.,* 1997; Fournier *et al.,* 1998a; Sekeyova *et al.,* 2001; Fournier *et al.,* 2003; Brouqui *et al.,* 2004). The *gltA* gene was less conserved in SFG rickettsiae, so it had a high discrimination power in *Rickettsia* spp. (Roux *et al.,* 1997). Regnery *et al.,* (1991) applied amplification of two *gltA* fragments to improve the species recognition. On the other hand, Roux *et al.* (1997) suggested that *OmpA* gene was specific for SFG rickettsiae. In another study the whole

*OmpA* gene was amplified and confirmed higher intra-SFG variability than that in *gltA* gene (Fournier *et al.,* 1998a). Moreover, intergenic spacers (*mppA*, *dksA* and *rpmE*) were characterised by high recognition, reproducibility, interpretation effortlessness and simplicity of joining of the information into open database (Parola *et al.,* 2005). These advantages of intergenic spacers were attributed to the variability of these spacers more than conserved, split and remnant genes (Fournier *et al.,* 2004).

In dogs, few molecular surveys were applied for canine SFG rickettsioses (Estrada-Pena & Venzal Bianch, 2006; Solano-Gallego *et al.,* 2006a). Levin *et al.* (2012) examined dogs by PCR and found that the great part of positive blood samples was recorded during the fever time and these results were reported also by Piranda *et al.* (2008). Solano-Gallego *et al.* (2008) reported that the percentage of rickettsial infection in the blood of sick dogs was 1.5% vs 14% in other studies (Estrada-Pena & Venzal Bianch, 2006; Torina *et al.,* 2007). Also, Kamani *et al.* (2013) detected DNA of *Rickettsia* spp. in dog blood samples (8.8%) and in their ticks (10.5%) in Nigeria.

To our knowledge, there are no studies detecting infection of rickettsiae in horses by molecular methods (PCR). Most of the prevalence surveys were done by using immunofluorescence for the detection of antibodies against different *Rickettsia* species in sera of horses (Lemos *et al.,* 1996; Horta *et al.,* 2004; Medeiros *et al.,* 2013; Alves *et al.,* 2014; Riveros-Pinilla *et al.,* 2015)

In camels, Kamani *et al.* (2015) identified *gltA* fragment (133 bp) of *Rickettsia* spp. in 18.8% of blood samples collected from camels in Nigeria. Wernery *et al.* (2001) demonstrated rickettsiae in blood films of camels using staining technique. Other studies in camels reported in the Canary Islands, Spain (Mentaberre *et al.,* 2013) affirmed that 83% of the examined camels were infected with *Rickettsia* spp. using ELISA. In Colombia, Santodomingo *et al*. (2018) detected *R. monacensis* and *R. bellii* in reptiles by using PCR and sequencing of the *gltA*, *16S rRNA*, and *sca1* genes.

In Egypt, there are few studies on animal hosts or humans, except the serosurvey of *R. conorii* infection which indicated that humans were exposed to SFG rickettsiae (Botros *et al.,* 1989; Corwin *et al.,* 1993). Moreover, Socolovschi *et al.* (2010) reported *R. siberica mongolitimonae* in a traveller from Egypt returned to France. Abdullah (2017) revealed that the infection rates of rickettsiae were 18%, 72% and 41% in dogs, horses, and camels, respectively by using PCR for amplification of *OmpA* and *gltA* genes. The author added that the phylogenetic analyses based on clustal omega suggested that detected rickettsiae sequences were *R. africae*-like in camels and dogs, and the first record of *R. massiliae*-like in dogs.

*Molecular diagnosis of rickettsiae in tick vectors*

Application of molecular tools for the detection of rickettsial infection in ixodid ticks was used as epidemiological tool (Parola & Raoult, 2001). Many studies all over the world were carried out for detection and identification of SFG rickettsiae on tick vectors by molecular methods (Guillemi *et al.,* 2015).

In North Africa, the most frequent circulating ticks were *Rh. sanguineus* and *Hyalomma* spp. (Bouattour, 2002). *Rickettsia conorii* was identified in *Rh. sanguineus* ticks from Algeria (Bitam *et*

*al.,* 2006; Bessas *et al.,* 2016), Tunisia (Sfar *et al.* 2009) and Morocco (Boudebouch *et al.,* 2009). Moreover, *R. aeschlimannii* was first detected in *H. marginatum* in Morocco (Beati *et al.,* 1997) and then detected by molecular tools in Algeria (Bitam *et al.,* 2006), Morocco (Sarih *et al.,* 2008) and Egypt (Abdel-Shafy *et al.,* 2012). *Rickettsia aeschlimannii* was also identified in other *Hyalomma* spp. including *H. dromedarii*, *H. impeltatum*, *H. rufipes*, *H. truncatum*, *H. aegyptium* and *H. excavatum* collected from camel and cow hosts in Egypt, Sudan, Algeria and Tunisia (Abdel-Shafy *et al.,* 2012; Demoncheaux *et al.,* 2012; Djerbouh *et al.,* 2012; Kernif *et al.,* 2012a; Leulmi *et al.,* 2016). Recently, *R. africae* was detected in *H. dromedarii* in infested camels in Algeria (Kernif *et al.,* 2012a) and Egypt (Abdel-Shafy *et al.,* 2012). *R. massiliae* was detected by PCR in *Rh. sanguineus* from Morocco (Sarih *et al.,* 2008; Boudebouch *et al.,* 2009); Algeria (Bitam *et al.,* 2006; Khaldi *et al.,* 2012; Bessas *et al.,* 2016; Leulmi *et al.,* 2016) and Tunisia (Khrouf *et al.,* 2014).

In Egypt, SFG rickettsiae were detected in *Rh. sanguineus* and *Hyalomma* species from Sinai (Lange *et al.,* 1992). Loftis *et al.* (2006a,b) detected *R. aeschlimannii* in *Hyalomma* spp. Recent studies reported for the first time *R. africae* and *R. aeschlimannii* in *H. dromedarii*, *H. impeltatum* and *H. marginatum* collected from camels in Sinai (Abdel-Shafy *et al.,* 2012; Abdullah *et al.,* 2016). The phylogenetic analyses of partial sequences of the two genes (*OmpA* and *gltA*) and sequences of three intergenic spacers (*mppA*, *dksA* and *rpmE*) of *Rickettsia* spp. in *H. marginatum* collected from a camel revealed a novel strain of *R. africae* (Abdullah, 2017).

In Brazil, Moerbeck *et al.* (2018) isolated *Rickettsia* sp. from the tick *Amblyomma nodosum*. They found that *Rickettsia* sp. was close to *Rickettsia* sp. strain NOD, with 99.9%, 100.0%, and 99.8% similarity for *gltA*, *htrA*, and *ompA* genes, respectively. In Australia, Chalada *et al.* (2018) used PCR and sequencing for molecular survey of *Rickettsia* spp in midguts of soft and hard ticks. They found *Rickettsia gravesii*, *Rickettsia felis*, and other *Rickettsia* spp. In Lithuania, *Rickettsia helvetica* was first detected in small mammals by sequencing of *gltA* gene and the 17 kDa protein coding gene (Mardosaitė-Busaitienė *et al.,* 2018). Kissenkötter *et al.* (2018) developed a rapid method for detecting *Rickettsia* spp. They targeted the 23S and 16S rRNA genes to develop a recombinase polymerase amplification assay that required between seven to ten minutes to amplify and detect one or ten DNA reactions.

## CONCLUSION

This review provides valuable information on all aspects of rickettsiae in animal hosts and their tick vectors. Some studies found that animals accompanying humans such as dogs, horses and camels could serve as reservoirs or carriers of the disease. The dogs are mainly infested by *Rh. sanguineus* that is the main vector of *R. conorii*, while horses and camels can be infested by other ixodid tick genera such as *Hyalomma*, *Amblyomma*, vectors of *R. africae* besides other *Rickettsia* spp. in Africa including Egypt. Therefore, people dealing with animals such as farmers and veterinarians should pay attention to ticks exposure that may be infected with rickettsiae. Tick control programmes have to be occasionally applied to avoid rickettsial infections to humans. Further

research studies are needed on a global scale to determine the biodiversity of *Rickettsia* spp. in domestic or wild animals and to detect their role in the distribution of ricketsioses. Climatic changes and animal movements between countries are the main challenges in diagnosis of rickettsiae. Therefore, it should investigate the animals and their tick vectors from time to time to monitor the epidemiology of the disease. The quick diagnosis helps appropriate decision to control the pathogens by treatment of infected animals or control of tick vectors.

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