

Review Article

A Review on Important Zoonotic Bacterial Tick-Borne Diseases in the Eastern Mediterranean Region

**Manijeh Yousefi Behzadi^{1,2}, Ehsan Mostafavi^{1,2}, Mahdi Rohani⁴, Ali Mohamadi¹,
Mozhgan Ahmadinezhad¹, Neda Moazzezy³, Masoomeh Shams-Ghahfarokhi⁵,
*Mehdi Razzaghi-Abyaneh⁶**

¹Department of Epidemiology and Biostatistics, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Tehran, Iran

²National Reference Laboratory of Plague, Tularemia and Q fever, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Akanlu, Kabudar-Ahang, Hamadan, Iran

³Molecular Biology Department, Pasteur Institute of Iran, Tehran, Iran

⁴Department of Microbiology, Pasteur Institute of Iran, Tehran, Iran

⁵Department of Mycology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

⁶Department of Mycology, Pasteur Institute of Iran, Tehran, Iran

***Corresponding author:** Prof. Mehdi Razzaghi-Abyaneh, mrab442@yahoo.com

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Abstract

Background: Zoonotic diseases as health concerns worldwide account for more than half of the emerging infectious diseases. Arachnids are powerful vectors to transmit several diseases to humans. Additionally, these emerging zoonotic diseases have been a considerable health threat in the Eastern Mediterranean Region of the WHO (EMRO) due to the large population living close to farms and international trade with nearby countries.

Methods: This review study is based on the reported three tick-borne diseases, Lyme disease, Tularemia, and Q fever, from Iran and other EMRO countries. To this end, we searched PubMed central, ISI web of Science, and Google with the related keywords in English at any time. The reported data are then sorted by countries for each disease.

Results: According to the published data, 15 countries in the region have one/more emerging infectious diseases. Q fever has been the most frequent infection in EMRO countries, while Lyme was less recorded. Furthermore, Iran is among the countries with documented history of all three investigated diseases.

Conclusion: Tick-borne disease is popular among EMRO countries, indicating that they have natural conditions for infections in animals and humans. It appears necessary to develop a disease management strategy and control programs against tick-borne diseases (TBDs). Moreover, the disease-resistant animal could be bred instead of susceptible livestock. Therefore, research studies to control TBDs should be regarded as a top priority plan.

Keywords: Tick-borne diseases, Tularemia, Lyme, Q fever, Mediterranean Region, Iran

Introduction

It is estimated that approximately one billion cases of illness and millions of deaths occur from zoonoses every year

worldwide. Moreover, 60% of globally reported emerging infectious diseases are zoonotic. During the last three decades,

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there were more than 30 new human pathogens from which 75% had originated from animals (1, 2). The tick-transmitted infections of humans, currently considered zoonoses, involve ticks and wild and/or domestic animal hosts with the maintained pathogens in natural cycles (3). Tick-borne diseases are among the crucial public health issues. There have been considerable efforts to control these infectious diseases worldwide. However, tick populations are increasing with geographic expanding ranges. They can transmit viral, parasitic, and bacterial pathogens, often harboring some agents simultaneously (4, 5). In fact, these arachnids play roles as powerful vectors transmitting several diseases, such as Lyme disease, tularemia, Q fever, and rickettsiosis. Therefore, surveillance of ticks and possible transmittable pathogens is a practical tool for a better prevention and control program within the epidemiological surveillance framework (6). The emerging zoonotic diseases are a considerable public health threat in the Eastern Mediterranean

Region of the WHO (EMR), which have been reported from 15 countries in the region often with bursting outbreaks in the last two decades (2). This region has been particularly prone to zoonotic infections due to the large population living rather close to animals and well-developed international trade with nearby countries (Table S1) (Fig. 1). Therefore, the region has remained at the crossroad of repeated outbreaks from emerging infectious diseases. Variable surveillance level and collaboration capacity of countries at the animal-human interface have mostly provoked these outbreaks (7, 8). These zoonotic infections result in global health concerns owing to their rapid spread possibility. Moreover, they impose economic consequences according to loss of economic opportunities through livestock loss (2, 9).

In this review on emerging tick-borne diseases, we focused on zoonotic bacterial infections, including Q fever, tularemia, and Lyme disease in EMRO countries based on the available reports and studies.

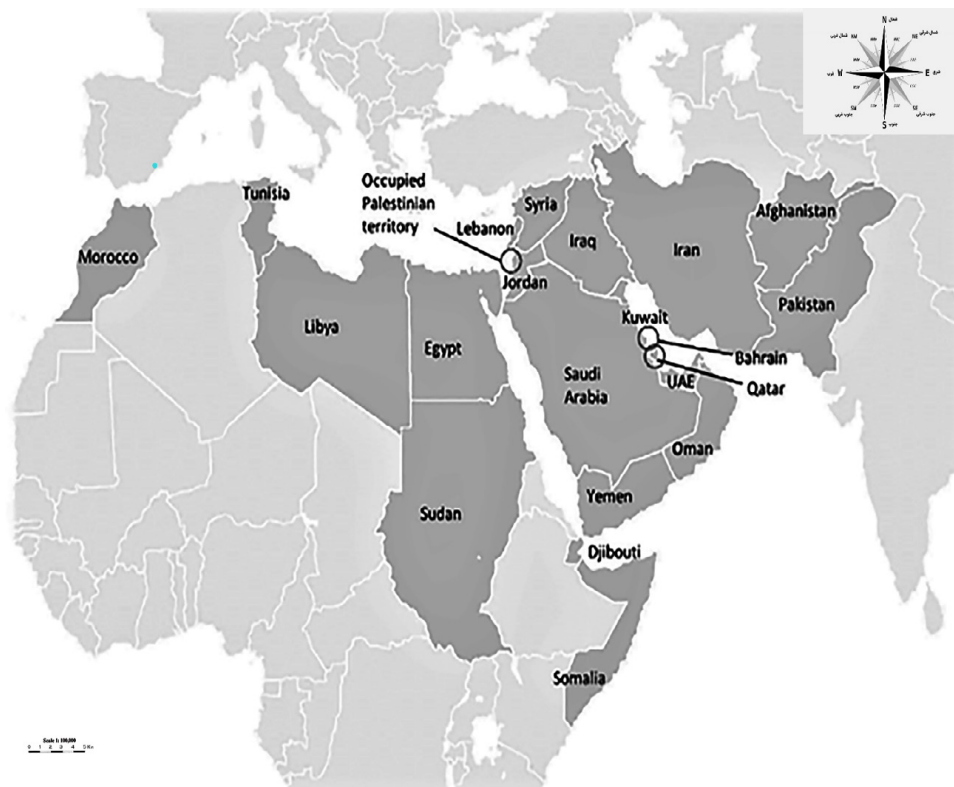


Fig. 1. Eastern Mediterranean Region (EMRO) (31)

Materials and Methods

We searched the databases PubMed, ISI web of sciences, and Google as the main international databases for the articles. The search strategy was based on the terms EMRO countries, tick-borne diseases, Tularemia, *Francisella tularensis*, Lyme disease, *Borrelia burgdorferi*, Q fever, and *Coxiella burnetii*, in English sources. The database search was performed in 2020 to obtain the related articles.

Results

The description of three diseases Tularemia, Lyme and Q fever in EMRO countries according to the literature reviewed is summarized in Table 1.

The summary of distribution of studied diseases in EMRO countries are shown in Fig. 2.

Tularemia

Tularemia is a zoonotic infection caused by *Francisella tularensis*, a gram-negative intracellular bacterium. This pathogen is a biological threat agent and can spread by aerosols and survive for months (39). However, no vaccine is available to prevent tularemia (40). The species *F. tularensis* is classically divided into four subspecies: Type A (*F. tularensis* subsp. *tularensis*), type B (*F. tularensis* subsp. *holarctica*), *F. tularensis* subsp. *mediasiatica*, and *F. tularensis* subsp. *novicida* (41, 42). Type A, which is most prevalent in North America, and type B, which is spread throughout the northern

hemisphere, are the main causative agents of tularemia worldwide. Type A usually causes more severe infection than type B, and its mortality rate is assessed 10–40 % in untreated patients (43).

Francisella tularensis infections have been identified in more than 250 animal species, including invertebrates and mammals (44). Multiple sources of infection have been documented, such as arthropod (ticks, flies, and mosquitoes), contaminated water, aerosol droplets, animal bites, and direct contact with their products (45). The reservoir of *F. tularensis* has not been known yet. Although outbreaks of the infection caused by type B are associated with a high rate of occurrence among lagomorphs and rodents, they do not appear to be capable of bacteria harboring between the outbreaks (32). The clinical presentation of tularemia in humans may vary from an asymptomatic level to severe diseases, which can cause death. After 3-5 days of the incubation period (ranging from 1 to 21 days), the infection often presents with flu-like symptoms, such as fever, chills, weakness, sore throats, joint pain, and headache. Then, the disease can evolve to glandular, ulceroglandular, pneumonic, oropharyngeal, oculoglandular, and typhoidal (41, 43). Ulceroglandular form is the most characteristic profile of the disease in which a papule develops and then becomes pustular and ulcerated at the tick bite site. Tularemia usually lasts over a period of 60-90 days if the treatment is not applied there. Antibiotics applied to treat the disease include streptomycin and ciprofloxacin, which usually last 10-21 days depending on the disease stage (6).

Table 1. Characteristic features of the three investigated tick-borne diseases

Disease	Bacteria	Tick vectors	Fatality rate	Approved vaccine	Ref.
Tularemia	<i>Francisella tularensis</i>	<i>Amblyomma</i> spp.	10-15%	N/A	(32-34)
		<i>Dermacentor</i> spp.			
		<i>Haemaphysalis</i> spp.			
		<i>Ixodes</i> spp.			
Q fever	<i>Coxiella burnetii</i>	<i>Haemaphysalis</i> spp.	19%	Q-VAX®	(35, 36)
		<i>Ixodes</i> spp.			
		<i>Rhipicephalus</i> spp.			
Lyme	<i>Borrelia burgdorferi</i>	<i>Dermacentor</i> spp.	Rare	VLA15	(37, 38)
		<i>Ixodes</i> spp.			

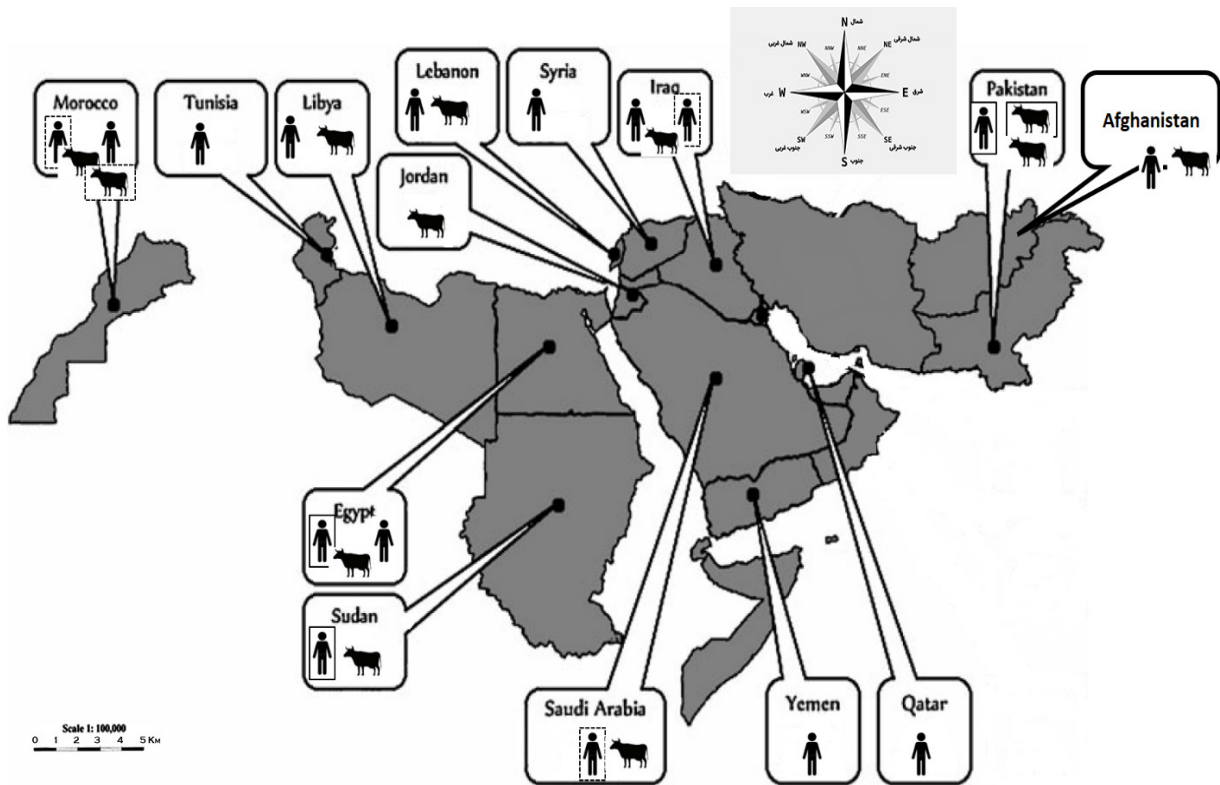


Fig. 2. The situation of the infection carriers in countries. The human and animal symbols are representative of the discussed infections in with picture border, without picture border and dot picture border for Tularemia, Q fever and Lyme respectively.

Iran

In 1973, the first positive serological tests were reported in domestic livestock and wild animals obtained from the south-eastern and north-western regions of Iran. This study aimed to detect *F. tularensis* from a small wild mammal’s spleens, which were then examined by a passive haemagglutination test. The test revealed a positive titer on the haemagglutination obtained from an Afghan hedgehog (*Hemiechinus megalofis*) collected around Zabol in eastern Iran (46). Tularemia was reported once in Afghanistan in a porcupine in 1973 (46, 47).

The first human case report was from southwestern Iran (47, 48). The assessment of tularemia presence in different groups (including hunters and healthcare workers) as well as in rodents from Kurdistan and Lorestan provinces exhibited positive anti-tularemia IgG antibodies (49, 50). Similar results were reported from the south-east in Sistan and Baluchistan Province (51) and

Chaharmahal va Bakhtiari Province (52). The serology assessment results of butchers and slaughterhouse workers from ten cities of Sistan and Baluchistan Province indicated that tularemia was endemic in this region (53). The data indicate that a high prevalence of tularemia in the neighboring countries of Iran, such as Armenia (54), Azerbaijan (55) and Turkey (56), could have high potential for human infections with *F. tularensis* in different parts of the country.

Egypt

In a study conducted in Egypt, a total of 319 ticks, along with blood and fecal samples were taken from camels and tested for the presence of *Francisella* spp. by PCR. Moreover, serum samples from 75 camel slaughterhouse workers were screened for the presence of *F. tularensis* IgG using the enzyme-linked immunosorbent assay. The prevalence of *Francisella* spp. was 4.7% among the ticks; however, it was not detected

in blood or fecal samples from camels, even camels carrying *Francisella* spp. positive ticks. On the contrary, seroprevalence of *F. tularensis* antibodies among the tested abattoir staff was estimated 9.3% with a significant prevalence among those frequently exposed to tick bites (57).

Sudan

There was the first case report of bacteremia caused by *F. tularensis* from the rural area of Southern Sudan, a 29-year-man who presented dry cough, shortness of breath, fever, and abdominal discomfort, along with pale and dehydrated. Coccobacilli were isolated by blood culture, which resulted in *F. tularensis* detection (48).

Yemen

The first study on collected ticks from livestock was conducted in which 34 isolated *Hyalomma marginatum* ticks were examined for the presence of pathogens using the molecular approach, which showed that three out of 34 samples were positive for the presence of *Francisella* spp. (59).

Pakistan

A total of 2280 soil samples were applied, representing several villages in Punjab Province, Pakistan. In addition, 6.22% of domestic animals were found to be positive in the seroconversion test. *Francisella tularensis* detection over a large geographic area indicated its extension to the enzootic range (60). In addition, the first report of *F. tularensis* isolation from a patient suffering from lung infection was reported in 2019 (61).

Q fever

Q fever as a zoonosis disease is caused by *Coxiella burnetii*, a strictly intracellular, gram-negative bacterium. Various species, including ticks, birds, and mammals are reservoirs of *C. burnetii*. This infection is mostly latent in animals, with durable bacteria shedding into the environment (62-64). Q fever can remain unrecognized due to poor surveillance of the disease.

Human is usually infected following birth or abortion, where the birthing fluids of an infected animal contaminate the environment (65). Abattoir workers, farmers, veterinarians and laboratory staff performing *C. burnetii* culture are at risk of Q fever (66, 67). Q fever may have different presentations, including an acute (febrile illness, pneumonia, or hepatitis) or a chronic disease (mainly endocarditis); however, it is often asymptomatic. The specific diagnosis of Q fever is based on serology tests. IgM and IgG antibodies can be detected 14-21 days after infection (68, 69).

Iran

Q fever is endemic in Iran like other Middle East countries (70, 71). The first acute Q fever case was documented in 1952 (72). In 1970, four other infected individuals were reported from Shiraz city (73), from 1970 to 1973, 45 acute Q fever subjects were also diagnosed from Abadan city in southwestern Iran (73). Furthermore, 80 Q fever patients were also documented from 1972 to 1976. After this time, the disease was neglected for more than thirty years, and no cases were reported until the first Q fever endocarditis was reported in Tehran in 2013 (74). The seroprevalence assessment of Q fever among slaughterhouse workers and butchers among different parts of Sistan va Baluchistan Province showed that Q fever survived among these workers in this area (75).

In a systematic review study in 2017, it was identified that the total distribution of Q fever in Iran was 27% in animals, mostly in goats and sheep. The contamination of dairy products was 5%. The results showed that higher positive PCR results in cattle but greater seropositivity in small ruminants. Therefore, *C. burnetii* related antibodies or DNA were frequently reported from ruminants in Iran, which could be a potential threat for human health and the livestock industry (71).

Afghanistan

Q fever was detected for the first time in Afghanistan in 2011 (76). The disease has

been known as an endemic threat to humans and animals in this country. Moreover, Q fever has been detected in American and English soldiers returning from Afghanistan (77).

Egypt

In a cross-sectional study between 2016 and 2017, it was shown that the prevalence of *C. burnetii* IgG antibodies in sheep, goats and humans was 25.68%, 25.20% and 25.71%, respectively. In humans, the only significant difference was higher positive infected women compared to men. No difference was found between the ruminants and humans (78). In another research, the prevalence of *C. burnetii* by specific antibodies was evaluated in 2,699 blood samples obtained from ruminants and camels. The specific antibodies were detectable mostly in camels (40.7%) followed by cattle (19.3%), buffaloes (11.2%), sheep (8.9%) and goats (6.8%). The seropositive results were dominant in animals older than four years. In addition, 8.7% of the living people in the related areas consumed raw camel milk from which no one had knowledge about Q fever. According to this study, exposure to *C. burnetii* was common in camels and ruminants, requiring increase of awareness among animal owners and veterinarians (79).

Sudan

The prevalence of *C. burnetii* antibodies in camels and cattle sera samples collected from nine states was investigated in a study in 2015. The overall of 29.92% prevalence of *C. burnetii* antibodies was obtained although an overall of 64.5% prevalence rate was observed in camels (80).

Saudi Arabia

The seroprevalence of Q fever in domestic livestock, including 630 sheep, 489 camels, 428 cattle and 423 goats, was assessed in 2018. The total seroprevalence was found to be 30.71%. Significant differences in seroprevalence were recorded

between the species, which were 51.53%, 30.67%, 34.04% and 12.38% in camels, cattle, goats and sheep, respectively. The domestic livestock and the camel were demonstrated to be the source of Q fever endemicity in Saudi Arabia (81). In the other study, 1310 serum samples were collected to examine antibodies of *C. burnetii*. The prevalence of *C. burnetii* among tested animals was 9.2%, which was most frequent among goats (15.6%). Moreover, old animals were 23 times more susceptible to *C. burnetii* ($P < 0.01$). *C. burnetii* infection was widespread among various ruminants of the eastern province of KSA, indicating a high risk for environmental contamination and the possible infection of humans and animals (82).

Pakistan

According to a cross-sectional study conducted in Punjab Province, determination of the prevalence and distribution of *C. burnetii* in soil was evaluated. The results demonstrated that in 47 samples of the total 2425 soil samples, *C. brunetti* DNA was detectable. The ELISA revealed an increase of antibodies in sheep (17.9%) and goats (16.4%). The correlation between soil DNA and *C. burnetii* antibodies in small ruminants showed that the odds of detecting these antibodies were significant in sheep [2.81 (95% CI: 1.20-7.37), $p = 0.02$]. This investigation provided the first evidence of *C. burnetii* presence in the environment in Punjab Province, Pakistan (83).

Qatar

A sero-epidemiological study in 2005 was conducted to estimate the seroprevalence of Q fever in two military groups, including one that resided in an area with the known history of Q fever epidemic and personnel from Central and Southwest Asia. The prevalence rate was found to be 7.2% and 2.1% in the first and second investigated groups, respectively. Nevertheless, there were no significant risk factors for Q fever seroconversion in either population (84).

Tunisia

The prevalence of the *C. burnetii* antibody among 500 sera from blood donors was tested, resulting in 26% confirmed antibodies against *C. burnetii* and indicating a high seroprevalence of Q fever in Tunisia (85).

Syria

In an investigation conducted between 1984 and 1988, Q fever was recorded in Czech workers in Syria. Moreover, there was a Belgian patient diagnosed with *C. burnetii* infection in this country (86).

Iraq

A study conducted from 1984 to 1988 in Iraq was identified that 42 Czech workers had Q fever (87). There was also an outbreak of this infection in 58% of marines in Iraq in 2005 (87). Furthermore, among 909 military personnel deployed in Iraq, antibody tests were performed against *C. burnetii*, and the data showed 10% of Q fever seroconversion, which was a significant infectious disease concern for the military personnel deployed in Iraq (88).

Jordan

The seroprevalence of *C. burnetii* was studied on-farm animals in 2019, and the data showed that on-farm biosecurity was crucially essential to reduce the transmission of the infection to humans and animals (89). Another study aimed to determine the prevalence of *C. burnetii* antibodies in the bulk reservoir milk obtained from dairy cattle, goats and sheep in the country. The positive result rate was 62.9% of the ruminant herds, which revealed the widespread exposure of Jordanian ruminants to the infection (89).

Lebanon

In 2018, the human seroprevalence of Q fever was aimed at evaluating *C. burnetii* antibodies among 421 serum samples. The result recorded the exposure of 37% to *C. burnetii* distributed in five provinces with the highest rate in two provinces of Bekaa and Akkar, and the lowest in Mount Lebanon (89).

Yemen

According to a survey to detect *C. burnetii* antibodies in approximately fifty veterinarians and butchers, 50 samples were examined from which three samples were positive, one was positive for phase 1, six were equivocal, which might have indicated the disease distribution in cattle and among professionals (90).

Libya

In 1951, an explosive outbreak of 25 cases of Q fever was recorded of which 22 were positive (91). Q fever was also documented in 48 Czech workers in Libya from 1984 to 1988 (92).

Morocco

Q fever outbreak was discovered in southern Morocco in 1947 where three *C. burnetii* strains were isolated from ticks and identified as *Hyalomma savignyi* Gerv. These ticks were widely prevalent among different domesticated animals (91). In 1951, outbreaks of Q fever were documented in six cities, and *C. burnetii* was isolated from gerbils and bovine ticks. In addition, 38% of infections were identified in people. Moreover, the prevalence was estimated to be 55%, 45%, and 38% in goats, cows and sheep, respectively (91). Furthermore, eight cases diagnosed with Q fever were recorded in the Medical Service of the Hospital of Meknes in Morocco in 1961 (93). Presence of *C. burnetii* in EMRO countries was shown in both humans and animals through different seroprevalence studies. However, more studies on tick species are needed in this region to identify the presence of *C. burnetii* in ticks in order to elucidate the role of different tick species in the Q fever transition and epidemiology.

Lyme disease

Lyme disease as a vector-borne disease is caused by spirochete *Borrelia burgdorferi*. The clinical presentation may vary depending on the illness stage, including erythema migrans, meningitis and cranial nerve palsies, carditis and arthritis. The infection

symptoms are relieved in the vast majority of individuals after proper cure application during 2-4 weeks. Serologic testing is often used to diagnose the infection; however, it sometimes results in misdiagnosis on blood samples from those with fatigue or arthralgia as non-specific symptoms. *B. burgdorferi* is transmitted by Ixodidae ticks, primarily by *Ixodes scapularis*, the deer tick in the United States. There are also other vectors to transmit the bacteria, including *Ixodes persulcatus*, *Ixodes ricinus* and *Ixodes pacificus* in Asia and Europe (94, 95). The experimental findings showed that in humans in which the *B. burgdorferi* transmission risk from ticks to humans was 25% for nymphal

ticks, which had fed for at least 72 hours. This declines to 0% for nymphal ticks that had fed less than 72 hours. The treatment for the early phase of the disease is based on a simple 10-14-day course of oral antibiotics application to eradicate the infection (96).

Iran

The Caspian Sea in Iran is the habitat for various hard tick species like *I. ricinus*, the notorious vector of Lyme borreliosis (LB). *Ixodes ricinus* and other hard ticks were examined, along with small mammals and common rodents for LB (Fig. 3). The ticks were collected from different mammalian hosts, including camels, sheep, dogs, goats,



Fig. 3. Iran map by its provinces. Only the names of the provinces in which the disease sample was discovered are mentioned. The human and animal symbols are representative of the discussed infections in with picture border, without picture border and dot picture border for Tularemia, Q fever and Lyme respectively.

and cattle. The real-time PCR sequence revealed that the *Borrelia* DNA in 14% of specimens (71 out of 501) belonged to *I. ricinus* and *Rhipicephalus* ticks. Nevertheless, none of the rodents nor small mammals had *Borrelia* infection (97).

Iraq

There was a case report from Iraq, a 28-year-old army male who presented with a rash on his anterior forearm for approximately 3 days. The clinical examination did not find any evidence of a bite mark, vesicles, induration or necrosis. The diagnosis of early localized Lyme disease was applied according to the erythema migrans as the unexpected solid case in 2010 (98).

Saudi Arabia

The only case report from this country was a 30-year-old male from a resident of Dammam in the eastern province of Saudi Arabia who presented an acute skin disease with a sudden onset. A red papule on his arm appeared, and the lesion quickly spread to a large size over a short time. The patient also complained of swelling and numbness of the upper arm, along with body ache, dizziness and unsteadiness. Finally, erythema migrans were diagnosed as a skin presentation of early localized LB (99).

Morocco

The prevalence of *Borrelia* infections was assessed from 2006 to 2011 on ticks, small mammals and thick blood films in patients. A considerable burrows proportion was infested with ticks of the *O. erraticus* complex with a mean of 39.5% among the whole country. *Borrelia* infections were found in 10.2% of the ticks and 8.6% of the rodents. Moreover, 102 tested patients were positive by thick blood film (100).

Conclusions

According to the published data, it is clear that tick-borne disease is common among EMRO countries, indicating that they have natural favorable conditions for

infections in animals and humans. Thus, they require disease management strategy development and control programs against tick-borne diseases (TBDs). Additionally, the movements of animals owing to trade or migration should be considered for having a probable infection as a risk of zoonoses. This policy must stem from the knowledge of the pathogen, host, and tick disease triangle concerning environmental changes, global warming, and the tick habitats' ecology and distributions. Recombinant vaccines to prevent the related infections and anti-tick agents can be applied to break this triangle, particularly in the case of animals. Disease-resistant animal promotion instead of susceptible breeds can be another approach. Therefore, further studies to control TBDs should be regarded as a top priority plan. The weakness of this study might be the keywords as well as the publications, which are not in English and are related to some unreported countries. A systematic and analytic review on this issue in EMRO countries may contribute to design a standard policy to achieve safer developing trades in the region.

Conflict of interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

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