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Review Article

Prevalence of Coxiella-infections in ticks - review and meta-analysis

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ABSTRACT

Q fever is a global zoonotic infection caused by the intracellular Gram-negative bacterium *Coxiella burnetii*. Historically, it is considered a vector-borne disease, but the role of ticks in transmission has not fully been elucidated yet. Excretion of *C. burnetii* in tick feces and saliva is well documented but the role of these findings or the epidemiological context is discussed controversially. Thus, the aim of this study was to determine the prevalence of *C. burnetii* DNA in ticks to clarify the potential role of tick species for maintenance of *C. burnetii* infection. A literature review was performed using Google scholar, Agora, Science Direct, PubMed and Scopus to identify original studies on *C. burnetii* DNA presence in ticks. The search was limited to literature published from 2009 to 2020 in English and French and focused on data obtained by molecular detection of *C. burnetii* DNA in ticks. Overall, the prevalence of *C. burnetii* in ticks collected in Africa varied from 2.91% to 13.97%, in Europe from 2.46% to 10.52% and the Middle East from 4.76% to 12.53%. Ticks collected from animals showed a prevalence of 8% (95% CI: 6%–10%), followed by ticks collected from the environment and animals of 7% (95% CI: 5%–10%). *C. burnetii DNA* has been found in samples of many tick species with the highest prevalence in *Rhipicephalus evertsi* and *Amblyomma variegatum.* However, most of these studies did not include a differentiation between *C. burnetii* and *Coxiella*-like endosymbionts making it finally difficult to estimate the potential role that ticks play in the epidemiology of Q fever. Therefore, it is necessary to analyze the vector competence of different tick species to transmit *C. burnetii*. Knowledge of the vector and reservoir competence of ticks is important for taking adequate preventive measures to limit infection risks.

1. Introduction

Q fever is a global zoonotic disease caused by the Gram-negative and obligate intracellular bacterium *Coxiella* (*C.*) *burnetii* (Abdel-Moein and Hamza, 2017) of the family *Coxiellaceae*, class Gammaproteobacteria, and phylum Proteobacteria (Angelakis and Raoult, 2010). *Coxiella burnetii* is reported as an emerging pathogen and considered as potential agent of bioterrorism (CDC, 2019). It survives under adverse environmental conditions such as high temperatures or dryness and stays infectious for a long period of time in the environment (Gürtler et al., 2014). It is one of the most contagious infectious agents known worldwide, uptake of 1 to 10 organisms via aerosols may result in disease in humans (Elliott et al., 2013). *Coxiella burnetii* is mainly transmitted via inhalation of contaminated aerosols and dust, which may arise from contaminated soil (Kersh et al., 2013). Ruminants are considered as the main reservoir for human infections. These animals shed bacteria with milk, amniotic fluid, urine, vaginal mucus and feces (Guatteo et al., 2011). *Coxiella burnetii* was originally isolated from a *Dermacentor andersoni* tick in 1938 in USA and since then ticks are discussed as vectors for transmission (Eldin et al., 2017). Of all acute human infections, 60% are asymptomatic but illness may be debilitating and is commonly presenting as a flu-like illness with high fevers and severe pneumonia or hepatitis (Roest et al., 2011). Chronic manifestations are rare but can be life-threatening and endocarditis is caused regularly. Animals are mainly asymptomatic or late term abortions, stillbirth, weak offspring, or fertility problems occur. In cattle mastitis is prominent. Therefore, infections with *C. burnetii* can cause loss of livestock and loss of productivity.

Ticks are recognized as the most important vectors of various pathogenic bacteria, protozoa, and viruses that cause disease in humans and animals worldwide (Colwell et al., 2011). Ticks may act as reservoirs of *C. burnetii* in nature (Sprong et al., 2012) and excretion of *C. burnetii* in tick feces after experimental infection has been shown for *Ixodes ricinus* and *Dermacentor marginatus* (Körner et al., 2020). *Coxiella burnetii* has

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been detected in more than 40 different tick species collected from different habitats such as vegetation as well as domestic and wild animals (Koka et al., 2018). Its DNA has been detected in tick species associated with humans and animals such as *Rhipicephalus sanguineus* (Watanabe et al., 2015), *I. ricinus* (Hildebrandt et al., 2010), *Dermacentor reticulatus* (Reye et al., 2013), *Haemaphysalis hystricis* and *Dermacentor steini* (Khoo et al., 2016), *Hyalomma lusitanicum* (González et al., 2020a) and *Amblyomma variegatum* (Ehounoud et al., 2016).The reported prevalence of *C. burnetii* in certain tick species in several countries may indicate that some tick species are able to transmit *Coxiellae*. However, the presence of *Coxiella*-like endosymbionts (CLE) in hard and soft ticks has been noted (Duron et al., 2017). These bacteria are genetically highly similar to *C. burnetii* and routine PCR detection assays cross react and can lead to misidentification (Duron et al., 2015). The aim of this study was to investigate the prevalence of *C. burnetii* in ticks collected from wild and domestic animals as well as from the environment in Africa, Europe and Middle East. This study assesses the role that ticks may play in transmission of *C. burnetii* to vertebrates, its maintenance and circulation in different epidemiologic settings.

2. Materials and methods

2.1. Search strategy

The review was planned and reported in accordance with guidelines for performing and reporting systematic reviews and meta-analyses (PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The literature search was performed from January to June 2020 using Google scholar, Agora, Science Direct, PubMed and Scopus to identify original studies on detection of *C. burnetii* DNA in ticks from 2009 to 2020. The following keywords 'Q Fever', 'Q-Fever', '*Coxiella burnetii*', '*C. burnetii*', 'ticks' and 'PCR' were used. Upon selection of potentially relevant articles, studies were analyzed according to main characteristics including study setting, agent of interest, study design and vector species. Reference Manager® was initially used for title and abstract screening of the articles. All titles and abstracts were examined by two authors and full-text articles were retrieved if they included data on the prevalence of *C. burnetii* DNA in ticks (Hoover et al., 1992). All data were extracted and subsequently transferred to Excel (Microsoft Corporation, Redmond, WA, United States).

2.2. Eligibility criteria and study selection

Several criteria were used to select eligible publications (1) the study was performed on ticks; (2) the results were accepted for IS1111 PCR assay (3) ticks were collected from animals and/or the environment. Another inclusion criteria was availability of the article in English or French language. The extracted data included: Year of publication, host, country of the study, sample size, number of cases, diagnostic tests, vector species and other pathogenic agents. Exclusion criteria for studies from the systematic review were: (1) lack of access to full article; (2) published as note and/or Letter to Editor. Extracted data were checked by two reviewers.

2.3. Quality assessment

As recommended by the Cochrane Collaboration, two assessors used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (Whiting et al., 2003). A table of quality score computation for each eligible publication was designed as follows: (1) Was the target population representative?, (2) Was the observation period well defined?, (3) Was some form of random selection used to select the samples?, (4) Diagnostic criteria, (5) Was the prevalence of *C. burnetii* DNA calculated for one or more tick species?, (6) Were ticks collected directly from animals or/and from the vegetation?

2.4. Data analysis

We conducted a meta-analysis for prevalence of *C. burnetii* DNA in tick species collected from animals and the vegetation. Heterogeneity among studies was evaluated by Cochrane Q and I2 statistical methods. A significant value ($p<0.05$) in the Cochrane Q method suggests a real effect difference in the meta-analysis. The outcome was measured and reported as prevalence with 95% confidence intervals. For pooled prevalence analysis, random effects model was adopted over fixed effect model because it is more robust when analyzing heterogeneous studies (Borenste et al. 2010) using the Statistical Software Package (STATA) Version 15.0 (StataCorp, College Station, TX, USA). The newly developed metaprop command was used (Nyaga et al., 2014).

3. Results

A total of 91 records were identified after removal of 88 studies as non-relevant based on the title of the articles. Thirty full-text articles were examined for eligibility and additional 15 full-text articles with out-of-scope studies were excluded. Finally, 15 studies were included in the meta-analyses as listed in Table 1 for African, Middle Eastern and European countries, respectively. Details of the studies included in this review are summarized in Fig. 1.

Only studies in which PCR was used to identify *C. burnetii* DNA in ticks were chosen. However, it should be noted that in most studies differentiation of *Coxiella*-like endosymbionts from *C. burnetii* was not performed. Studies meeting the criteria have been found for six African countries i.e., Egypt, Ethiopia, Kenya, Nigeria, Senegal and South Africa, one for the Middle East and three for European countries i.e., Serbia, Slovakia and Spain (Table 1). The prevalence of *C. burnetii* DNA in ticks collected in Africa varied from 2.91% to 13.97% and for European and Middle Eastern countries from 3.01% to 12.53% (Table 1).

The random effect model was used in the meta-analysis because of heterogeneity among the data which were included in this study ($I^2 = 93.15$, Chi-square $= 185.21$, df $= 24$ and $P < 0.05$) with an overall estimated prevalence at 7% (95% CI: 5%– 10%). The overall prevalence of *C. burnetii* DNA identified in tick samples collected in the Middle East, Africa and Europe was 10% (95% CI: 7%– 13%), 8% (95% CI: 5%– 11%) and 6% (95% CI: 3–9%), respectively (Fig. 2). Detection of *C. burnetii* DNA, showed a prevalence of 8% (95% CI: 6%–10%) in ticks collected from animals, followed by ticks collected from the environment and animals, which was 7% (95% CI: 2%–11%) (Fig. 3). In this study, *C. burnetii* DNA was identified in 24 different tick species with notable prevalences of *R. evertsi* (41%), collected in Kenya, Nigeria, Senegal, followed by *A. variegatum* (11%) collected mainly in Ethiopia, Nigeria and Senegal and *R. pulchellus* (7%) collected in Egypt, Ethiopia and Kenya (Fig. 4).

4. Discussion

Worldwide, tick-borne diseases have gained more attention for public health and veterinary medicine in recent years. Ticks are the second most important vectors after mosquitos and are able to transmit a higher number of different pathogens than any other arthropod (Socolovschi et al., 2012). *Coxiella burnetii,* the etiological agent of Q fever, is discussed as tick-borne disease (Shipman et al., 2013). *Coxiella burnetii* DNA has been found in many species of ticks in the world (Körner et al., 2021) but little information on the role of ticks in transmission of *C. burnetii* is available. Additionally, with discovery of *Coxiella*-like endosymbionts and possible misidentification by routine PCR detection assays, the real prevalence of *C. burnetii* in ticks may be misinterpreted. However, some studies such as those of Varela Castro et al. (2018) on *Rhipicephalus* (*R.*) *sanguineus, R. bursa, Hyalomma* (*H.*) *sulcata, Haemaphysalis (Hae.), punctata* and *D. marginatus* imply a possible role of ticks in the eco-epidemiology of *C. burnetii* Varela Castro et al. (2018). concluded that a role as classic vectors can neither be proposed nor ruled

Table 1
Characteristics of included studies in the review.

Region	Country	Reference	Geographical area	Year of study	Host	Number of ticks examined	Prevalence of *C. burnetii* DNA in ticks (%)	PCR assay or sequencing	Tick species
Africa	Algeria	(Bellabidi et al., 2020)	Ouargla/El Oued/ Biskra	2018-2019	Camel	60	7(11.66)	sequencing	*Hyalomma dromedarii/ Hyalomma impeltatum/ Hyalomma excavatum*
	Egypt	(Ghoneim et al., 2020)	Cairo	NA	Dromedary/Camel	370	20(5.40)	sequencing	*Hyalomma dromedarii/ Amblyomma hebraeum/ Rhipicephalus pulchellus/ Hyalomma anatolicum/ Amblyomma variegatum/Amblyomma gemma/Rhipicephalus*
	Ethiopia	(Kumsa et al., 2015)	Oromia	2011-2014	Cattle/Sheep/Dogs/ Cats	842	54(6.41)	sequencing	*Amblyomma gemma/ Rhipicephalus pulchellus/ Hyalomma marginatum rufipes/Amblyomma variegatum/Amblyomma cohaerens/Rhipicephalus praetextatus/Rhipicephalus decoloratus*
	Ethiopia	(Sulyok et al., 2014)	Didessa valley	2012	Cattle	296	32(10.81)	sequencing	*Amblyomma variegatum/ Amblyomma cohaerens/ Amblyomma lepidum/ Rhipicephalus decoloratus/ Rhipicephalus evertsi/ Rhipicehalus praetextatus/ Hyalomma marginatum rufipes*
	Kenya	(Koka et al., 2018)	Marigat/Mai Mahiu/Ijara/ Garissa/Isiolo	2011-2012	Sheep/Goats/Cattle	380	21(5.52)	PCR assay	*Amblyomma gemma/ Rhipicephalus appendiculatus/ Rhipicephalus pulchellus/ RhipicephalusR. evertsi*
	Kenya	(Ndeereh et al., 2017)	Laikipia/Maasai/ Mara/National Reserve	2014-2015	Buffalo/ Burchell's/ Grant's gazelle / common waterbuck/ Eastern black Rhinoceros/Impala/ Topi/Coke's hartebeest / Wildebeest/Blue	137	4(2.91)	sequencing	*Rhipicephalus appendiculatus/ Rhipicephalus pulchellus/ Rhipicephalus evertsi*
	Nigeria	(Reye et al., 2012)	Elepo/Alowo-nle/ Fuleni/ Orisunbare/ Lanlate/Maya/ Igbo-Ora/Moniya/ Alakia/Bodija/ Mokola	2009	Vegetation/Cattle	136	19(13.97)	sequencing	*Amblyomma variegatum/ Rhipicephalus annulatus/ Hyalomma impeltatum/ Rhipicephalus Rhipicephalus evertsi*
	Senegal	(Mediannikov et al., 2010)	Sine-Saloum region/Niakhar region/ southeastern	2009	Cattle/ Goats/ Sheep/ Horses/Donkeys	2893	365(12.61)	sequencing	*Amblyomma variegatum/ Rhipicephalus annulatus/ Hyalomma marginatum rufipes/Hyalomma truncatum/Rhipicephalus evertsi/Rhipicephalus guilhoni*
	South Africa	(Mtshali et al., 2015)	Eastern Cape/Free State/KwaZulu-Natal/ Mpumalanga	NA	Cattle/Sheep/Goats	590	42(7.11)	sequencing	*Rhipicephalus evertsi/ /Amblyomma hebraeum/ Rhipicephalus decoloratus*
Europe	Serbia	(Bogunovic et al., 2018)	Belgrade	2011	Dogs	228	24(10.52)	sequencing	*Rhipicephalus sanguineus*
	Slovakia	(Spitalská et al., 2018)	Zohor/ Gabčíkovo/ StaráLesná/ Hrhov	2012-2017	Vegetation	497	15(3.01)	sequencing	*Dermacentor reticulatus/ Ixodes ricinus/ Haemaphysalis inermis*
	Slovakia	(Knap et al., 2019)	Čiginj/Volče/ Dolenja vas/ Mačkovci/ Maribor/Senožeče/ Vremščica/ Žirovnica	2009	Vegetation/Cattle/ Wildlife	691	17(2.46)	PCR assay	*Ixodes ricinus/ Haemaphysalis punctata*
	Spain	(Bolaños-Rivero et al. 2017)	Canary Islands	2010-2011	Vegetation /Livestock /Dogs/	377	23(6.10)	PCR assay	*Rhipicephalus turanicus/ Hyalomma lusitanicum/ Rhipicephalus sanguineus*

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Table 1 (*continued*)

Region	Country	Reference	Geographical area	Year of study	Host	Number of ticks examined	Prevalence of *C. burnetii* DNA in ticks (%)	PCR assay or sequencing	Tick species
Middle East	Iran	(Ghashghaei, et al. 2017)	Sistan/Baluchestan	2014-2015	Lagomorphs/ Hedgehogs/Birds Cattle	84	4(4.76)	PCR assay	*Hyalomma anatolicum/ Hyalomma excavatum/ Rhipicephalus sanguineus*
	Iran	(Khalili et al., 2018)	Kerman	2012-2013	Dogs	375	47(12.53)	sequencing	*Rhipicephalus sanguineus*

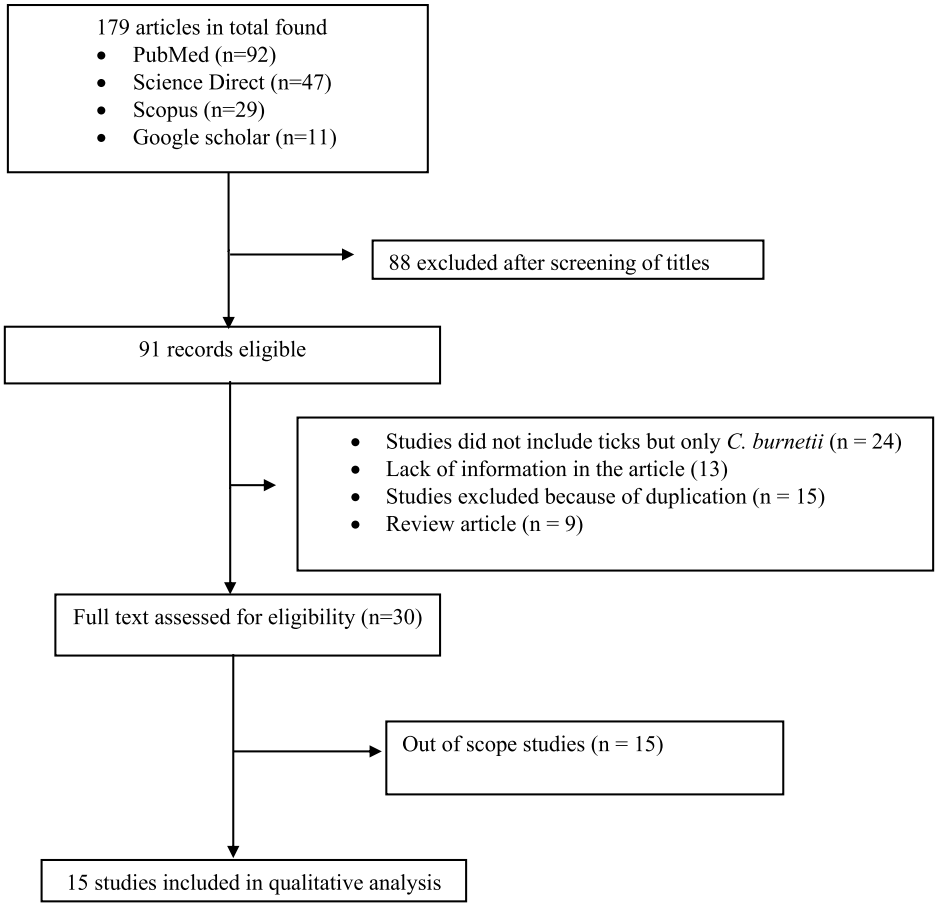

Fig. 1. Decision process to include and exclude articles to this systematic review.

out, but that factors promoting vectorial capacity exist. The work of Siroký et al. (2010) showed transmission of *C. burnetii* from *H. aegyptium* larvae fed on experimental *Coxiella*-infected guinea pigs to uninfected guinea pigs through feeding of molted nymphs. Experimental transmission of *C. burnetii* from infected to uninfected animals via tick bite has been demonstrated for *Ornithodoros (O.) moubata, I. holocyclus, Hae. bispinosa,* and *R. sanguineus* (Smith 1942a, 1942b). The contribution of ticks to the epidemiology of *C. burnetii* deserves further attention but vector competence of ticks has not yet been fully evaluated (Sprong et al., 2012). It can also be speculated that bacteria in tick feces dry up and the resulting infection is airborne considering the low infection dose of 1 to 10 *Coxiellae* (Elliott et al., 2013). After having fed on septicemic mammalian hosts ticks would then pose a potential danger to domestic and wild animals. Several studies have reported its presence in different parts of ticks such as in the midgut, hemolymph (Lang, 1990), feces (Philip, 1948) as well as transstadial transmission of *C. burnetii* (Smith and Derrick 1940). *Coxiella burnetii* undergoes a morphological differentiation from the replicative intracellular large cell variant to the small cell variant with spore-like attributes. It survives for long periods e.g. at room temperature and in tick feces (Philip, 1948). *Coxiella burnetii* can cause abortions and reproductive disorders in animals (Ruiz-Fons et al., 2010). However, the ability of ticks to transmit *C. burnetii* is controversial. The studies of Davis et al. (1938), who isolated the highly-virulent *C. burnetii* Nine Mile strain from a *D. andersoni* tick, proof only the presence of the virulent agent in the tick but allow no conclusion on vector competence of this tick. This isolate is used as laboratory reference strain until today.

The detection of *C. burnetii* DNA in tick species collected from wild or domestic animals and the environment indicates considerable implications in the epidemiology of *C. burnetii*. Studies done with PCR only before 2015, when Duron described the presence of CLE in ticks and cross reaction of the IS1111 PCR detection assay for the first time must be interpreted with caution. This is also true for PCR studies without sequencing of the PCR amplicons after that time point (Duron, 2015;

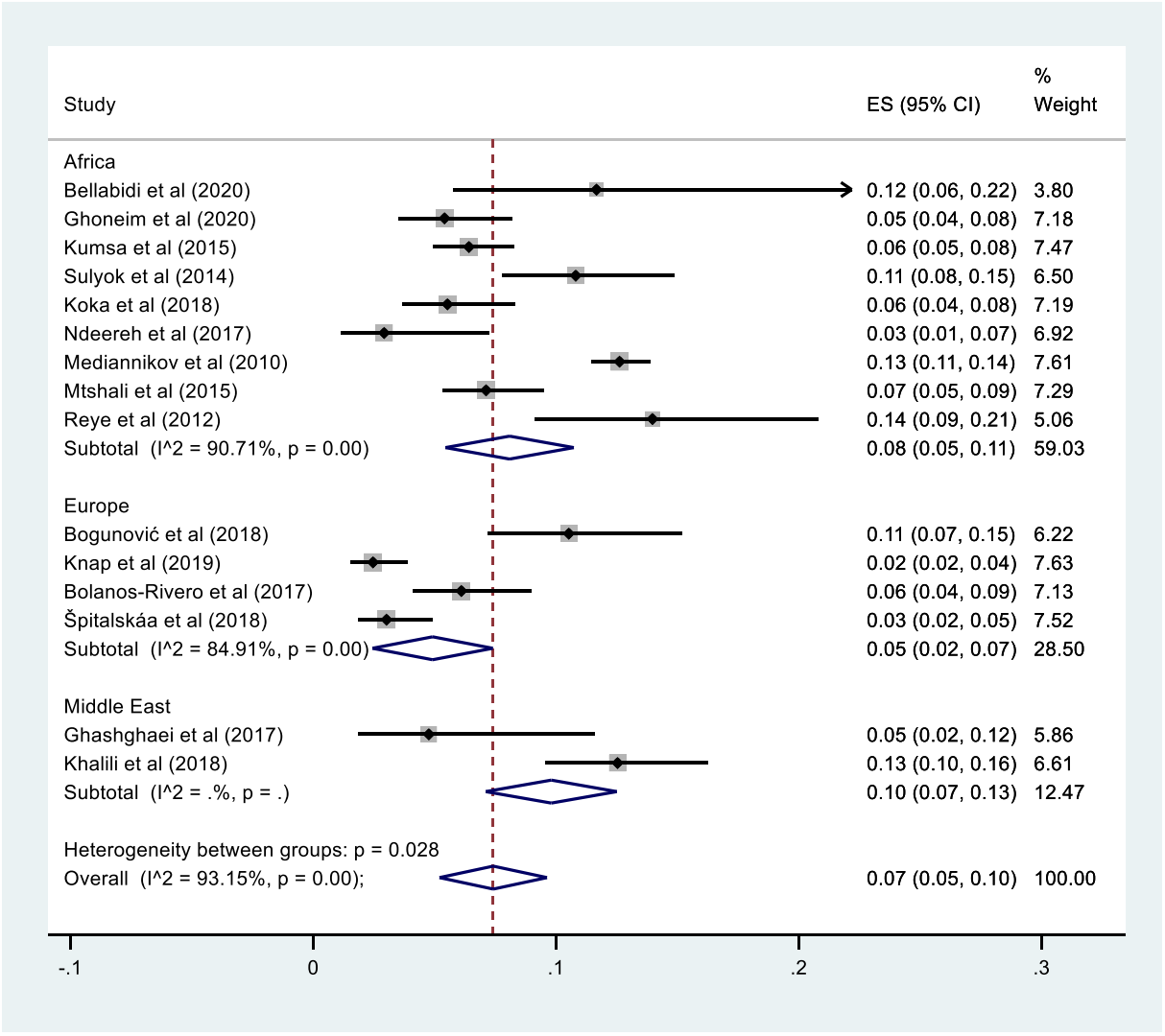

Fig. 2. Forest plot showing stratified prevalence studies on *Coxiella burnetii* DNA in ticks in Africa, Europe and Middle East.

Jourdain et al., 2015; Seo et al., 2016). A prevalence of 2% CLE in *H. longicornis* and *R. microplus* ticks was reported (Lee et al., 2004; Muramatsu et al., 2014). Recent studies carried out in China using next-generation metagenomic sequencing (mNGS), revealed that 8.33% of analyzed *R. microplus* ticks are positive for CLE. This demonstes the symbiotic relationship between CLE and ticks (Jiao et al., 2021). Reports by Ben-Yosef et al. (2020) showed the presence of CLE is primarily required for blood meals and egg production. Thus, CLEs were phylogenetically closely associated with their tick hosts. The difference between *C. burnetii* and CLE, detected in various tick species around the world, suggests that these bacteria do not follow a co-evolution model in ticks (Machado-Ferreira et al., 2016). For the moment these authors assume, that *C. burnetii* DNA prevalence beyond this threshold can be considered as indicative for prevalence of *C. burnetii* DNA in tick samples. Here, future studies need to shed further light on the prevalence of CLE in different tick species from different ecosystems. Studies of Mantovani and Benazzi (1953), identified *C. burnetii* in *R. sanguineus* ticks collected from an infected dog feeding on *C. burnetii* positive after birth materials, demonstrating uptake of *C. burnetii* via the blood meal. In this study, the prevalence of *C. burnetii* DNA reported in the literature, varies according to tick species, hosts and sampling area. In a study conducted in Algeria by Leulmi et al. (2016), *C. burnetii* DNA was detected using the IS1111 element and IS30a spacers PCRs in 15.8 % of *I. vespertilionis* ticks collected from bats. Studies in Russia and Bulgaria revealed the presence of *C. burnetii* DNA (16S rRNA) in ticks collected from wild birds (Tokarevich et al., 2019). In Cuba detection and sequencing of the IS1111 elements allowed the identification of *C. burnetii*-specific DNA in *A. mixtum* collected from a horse (Noda et al., 2016). The study conducted by (Psaroulaki et al., 2014) showed a high prevalence of *C. burnetii* DNA in ticks collected from hares (40%) and from mouflons (25.2%) in Cyprus. The results of Pacheco et al. (2013) showed that ticks may present an important reservoir for *C. burnetii* due to high DNA prevalence. They were able to isolate *C. burnetii* from tick samples and concluded that ticks may play an essential role in the enzootic cycle of ticks in Argentina. The works of Satta et al. (2011) show the presence of *C. burnetii* DNA by detection of the *sod* gene in *R. sanguineus, R. turanicus* and *H. sulcata* collected from wild and domestic animals in Italy and Knobel et al. (2013) by detection of the IS1111 element in *H. leachi* ticks collected from domestic dogs in Kenya. Samples of ticks collected from domestic animals (goats, sheep) in Southeast Iran have been positive for *C. burnetii* DNA based on IS1111 (Fard and Khalili, 2011). A study conducted on hard tick species found on camels shed light on the likely potential role of ticks in transmitting *C. burnetii* to these animals (Ghoneim et al., 2020). In Algeria, Bellabidi et al. (2020) reported aprevalence of 11.66% of *C. burnetii* DNA by genotypic analysis of the IS1111 element in ticks collected of camels. In *A. varigatum* from North-central Nigeria *C. burnetii* DNA was found in 25% ticks analyzed (Ogo et al., 2013). These studies have shown that the

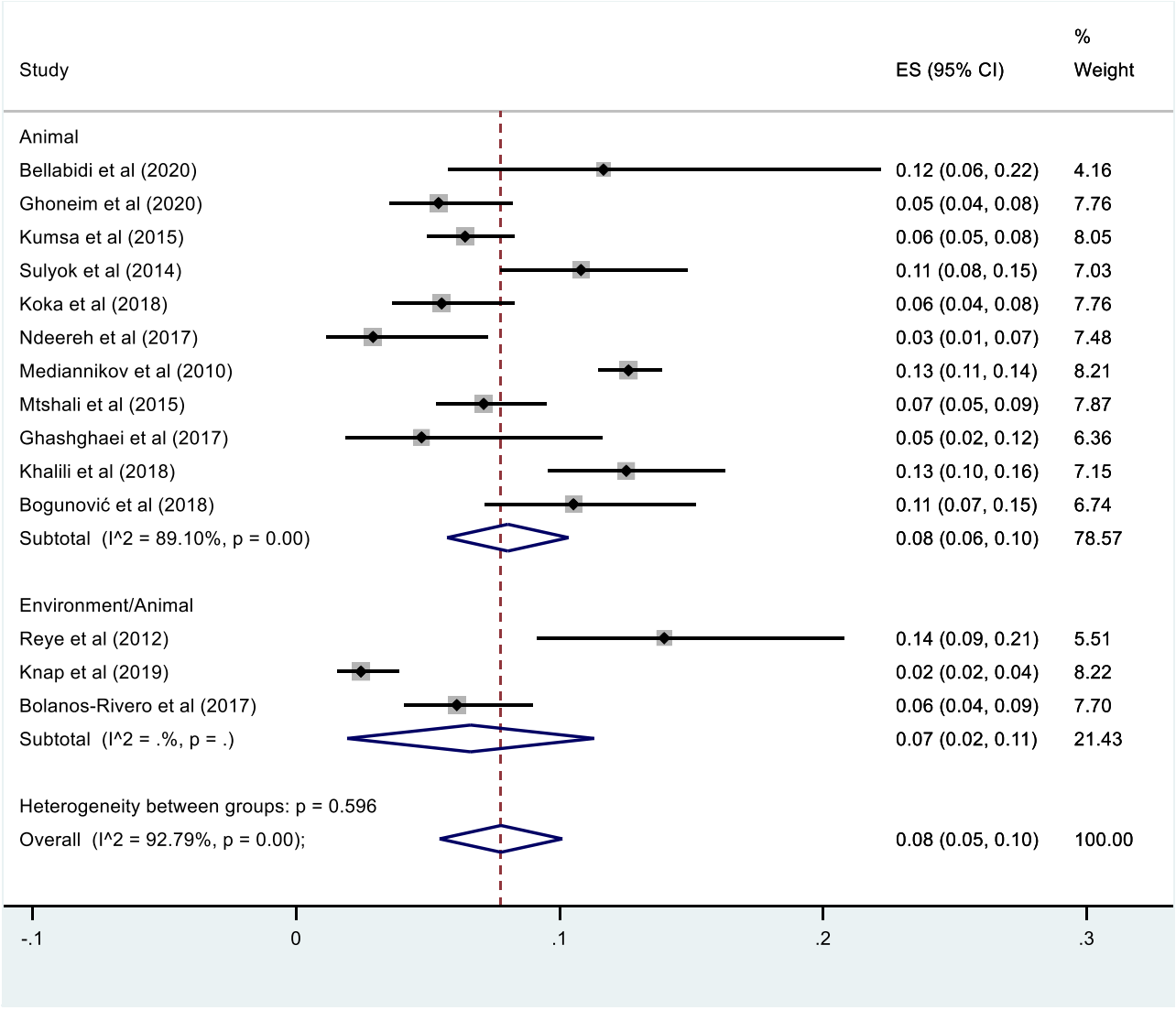

Fig. 3. Forest plot showing stratified prevalence studies on *Coxiella burnetii* DNA in ticks collected from animals and environment/animals.

prevalence of *C. burnetii* vary with tick species. In a study in Germany, the prevalence of *C. burnetii* DNA infections in *I. ricinus* ticks collected in a forest region was 1.9% based on detection of the IS1111 element (Hildebrandt et al., 2010). This area needs to be reinvestigated with appropriate techniques. Prevalence of *C. burnetii* DNA (IS1111) in ticks collected from wild animals (6%), domestic dogs (6.9%) and livestock (11.3%) in Spain (Bolaños-Rivero al. 2017) was evaluated. Others studies in Spain have shown that 50.45% of ticks collected from negative hosts were positive to *C. burnetii* DNA, suggesting that the pathogen probably was acquired at a previous tick stage implying transstadial transmission(González et al., 2020b). In these settings tick feces can be highly infectious to domestic animals and a source for human infection (Fard and Khalili, 2011). In Ivory-Coast, *C. burnetii* has been identified by IS1111 and IS30A in *A. variegatum* collected from vegetation (Ehounoud et al., 2016). Similar results have been observed in Oyo state, South West Nigeria where ticks collected from vegetation were positive for the *htpB* gene of *C. burnetii* (Reye et al., 2012) and also for the IS1111 element in France (Bonnet et al., 2013). Thus, if ticks play an important role in the spread, propagation and maintaining of *C. burnetii* in the environment is still inconclusive due to possible misidentification with CLE. In addition *C. burnetii* has been identified in ticks as well as in hosts in several studies (Bellabidi et al., 2020; Knap et al., 2019) Kumsa et al. (2015). showed the importance of tick populations in the maintenance of this zoonotic pathogen, by reporting the presence of *C. burnetii* DNA (detection of IS1111 and multispacer sequence typing, MST) in *A. gemma, R. decoloratus, R. pulchellus, H. (m) rufipes, A. cohaerens, and R. praetextatus* in Ethiopia. Ticks can serve as sentinel of *C. burnetii* in an area. Collections of hard and soft ticks in different areas in Senegal have allowed to identify *C. burnetii* DNA (detection of IS1111 and IS30A, MST) in *A. variegatum, R. decoloratus, H. (m) rufipes, H. truncatum, R. evertsi, R. guilhoni, R. annulatus* and *O. sonrai* (Mediannikov et al., 2010). The overall presence of *C. burnetii* in many tick species implies an important role of this vector in the epidemiology of this zoonotic disease but the local setting in rural countries has be taken in consideration e.g. positive ticks of cattle in a pastoralist setting will have a totally different impact on human health than those ticks found in a remote forest without contact to humans or farm animals in European countries. Although the role of ticks in the transmission of *C. burnetii* is controversial, this study demonstrates the need for epidemiological surveillance of Q fever using appropriate sequencing tools, which is a problem for health care in many developing countries. Knowledge on vector competence of local tick species is important to control and prevent this and other diseases.

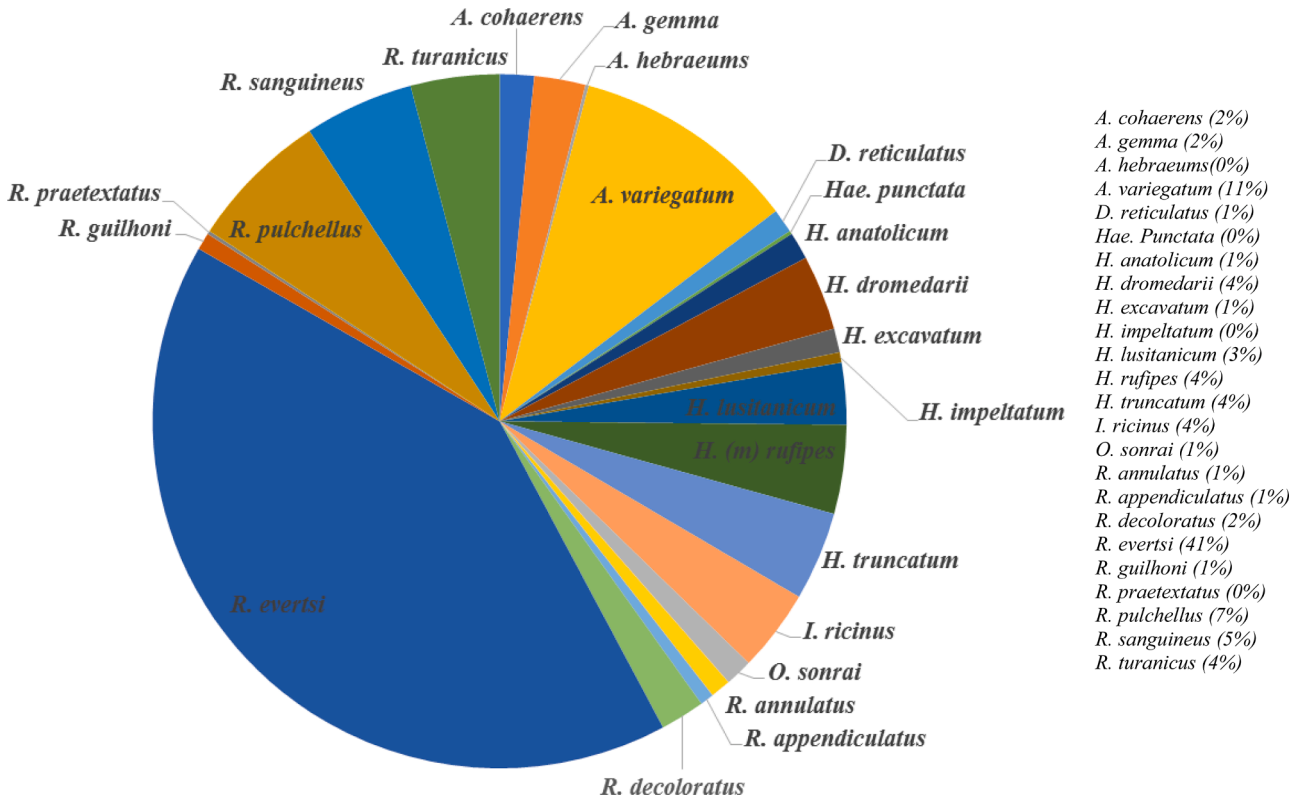

Fig. 4. Detection of *C. burnetii* DNA in different tick species.

5. Conclusion

Coxiella burnetii DNA has been identified by IS1111 PCR in many tick species worldwide. Most of these studies could be challenged because of the possibility of misidentification of *Coxiella*-like endosymbionts and *C. burnetii* by PCR. Here, ticks infected with *C. burnetii* may present a risk for infection of animals and humans via fecal aerosols coming from ticks fed on septicemic hosts. The presence of *C. burnetii* in ticks of different bioclimatic areas and many socioeconomic settings indicate their potential role in the local epidemiology of Q fever. A future task of public health and veterinary public health officers will be to analyze the vector competence of local tick species, to make a reasonable risk assessment for the role of these ticks in the transmission of *C. burnetii*. This information is essential to prevent Q fever, as treatment remains difficult and the morbidity high.

Declaration of Competing Interest

Authors declare no conflict of interests

References

Abdel-Moein, K.A., Hamza, D.A., 2017. The burden of *Coxiella burnetii* among aborted dairy animals in Egypt and its public health implications. Acta Trop. 166, 92–95. https://doi.org/10.1016/j.actatropica.2016.11.011.

Angelakis, E., Raoult, D., 2010. Q fever. Vet. Microbiol. Zoonoses: Advances and Perspectives 140, 297–309. https://doi.org/10.1016/j.vetmic.2009.07.016.

Bellabidi, M., Benaissa, M.H., Bissati-Bouafia, S., Harrat, Z., Brahmi, K., Kernif, T., 2020. *Coxiella burnetii* in camels (*Camelus dromedarius*) from Algeria: Seroprevalence, molecular characterization, and ticks (Acari: Ixodidae) vectors. Acta Trop. 206, 105443 https://doi.org/10.1016/j.actatropica.2020.105443.

Ben-Yosef, M., Rot, A., Mahagna, M., Kapri, E., Behar, A., Gottlieb, Y., 2020. *Coxiella*-like endosymbiont of *Rhipicephalus sanguineus* is required for physiological processes during ontogeny. Front. Microbiol. 11, 493.

Bogunovic, D., Stević, N., Sidi-Boumedine, K., Misic, D., Tomanović, S., Kulišić, Z., Magas, V., Radojicic, S., 2018. Molecular Evidence of Q Fever Agent *Coxiella Burnetii* in Ixodid Ticks Collected from Stray Dogs in Belgrade (Serbia). Acta Vet. (Beogr.) 68, 257–268. https://doi.org/10.2478/acve-2018-0023.

Bolaños-Rivero, M., Carranza-Rodríguez, C., Rodríguez, N.F., Gutiérrez, C., Pérez-Arellano, J.-L., 2017. Detection of *Coxiella burnetii* DNA in peridomestic and wild animals and ticks in an endemic region (Canary Islands, Spain). Vector-Borne Zoonotic Dis 17, 630–634.

Bonnet, S., de la Fuente, J., Nicollet, P., Liu, X., Madani, N., Blanchard, B., Maingourd, C., Alongi, A., Torina, A., Fernández de Mera, I.G., Vicente, J., George, J.-C., Vayssier-Taussat, M., Joncour, G., 2013. Prevalence of tick-borne pathogens in adult *Dermacentor spp*. ticks from nine collection sites in France. Vector Borne Zoonotic Dis. Larchmt. N 13, 226–236. https://doi.org/10.1089/vbz.2011.0933.

Colwell, D.D., Dantas-Torres, F., Otranto, D., 2011. Vector-borne parasitic zoonoses: emerging scenarios and new perspectives. Vet. Parasitol. 182, 14–21.

Davis, G.E., Cox, H.R., Parker, R.R., Dyer, R.E., 1938. A filter-passing infectious agent isolated from ticks. Public Health Rep. 53, 2259–2311.

Duron, O., 2015. The IS1111 insertion sequence used for detection of *Coxiella burnetii* is widespread in *Coxiella*-like endosymbionts of ticks. FEMS Microbiol. Lett. 362, fnv132.

Duron, O., Binetruy, F., Noël, V., Cremaschi, J., McCoy, K.D., Arnathau, C., Plantard, O., Goolsby, J., Pérez de León, A.A., Heylen, D.J., 2017. Evolutionary changes in symbiont community structure in ticks. Mol. Ecol. 26, 2905–2921.

Duron, O., Noël, V., McCoy, K.D., Bonazzi, M., Sidi-Boumedine, K., Morel, O., Vavre, F., Zenner, L., Jourdain, E., Durand, P., 2015. The recent evolution of a maternally-inherited endosymbiont of ticks led to the emergence of the Q fever pathogen, *Coxiella burnetii*. PLoS Pathog 11, e1004892.

Ehounoud, C., Kouassi Patrick, Y., Dahmani, M., Achi, L., Amanzougaghene, N., N'Douba, A., Jean David, N., Raoult, D., Fenollar, F., Mediannikov, O., 2016. Multiple Pathogens Including Potential New Species in Tick Vectors in Côte d'Ivoire. PLoS Negl. Trop. Dis. 10, e0004367 https://doi.org/10.1371/journal.pntd.0004367.

Eldin, C., Melenotte, C., Mediannikov, O., Ghigo, E., Million, M., Edouard, S., Mege, J.-L., Maurin, M., Raoult, D., 2017. From Q fever to *Coxiella burnetii* infection: a paradigm change. Clin. Microbiol. Rev. 30, 115–190.

Elliott, A., Peng, Y., Zhang, G., 2013. *Coxiella burnetii* interaction with neutrophils and macrophages in vitro and in SCID mice following aerosol infection. Infect. Immun. 81, 4604–4614.

Fard, S.N., Khalili, M., 2011. PCR-Detection of *Coxiella burnetii* in Ticks Collected from Sheep and Goats in Southeast Iran. Iran. J. Arthropod-Borne Dis. 5, 1–6.

Ghashghaei, O., Nourollahi Fard, S.R., Khalili, M., Sharifi, H., 2017. A survey of ixodid ticks feeding on cattle and molecular detection of *Coxiella burnetii* from ticks in Southeast Iran. Turk. J. Vet. Anim. Sci. 41, 46–50. https://doi.org/10.3906/vet-1601-83.

Ghoneim, N.H., Abdel-Moein, K.A., Zaher, H.M., Abuowarda, M.M., 2020. Investigation of Ixodidae ticks infesting camels at slaughterhouse and its potential role in transmitting *Coxiella burnetii* in Egypt. Small Rumin. Res. 191, 106173 https://doi.org/10.1016/j.smallrumres.2020.106173.

González, J., González, M.G., Valcárcel, F., Sánchez, M., Martín-Hernández, R., Tercero, J.M., Olmeda, A.S., 2020a. Transstadial transmission from nymph to adult of *Coxiella burnetii* by naturally infected *Hyalomma lusitanicum*. Pathogens 9, 884.

González, J., González, M.G., Valcárcel, F., Sánchez, M., Martín-Hernández, R., Tercero, J.M., Olmeda, A.S., 2020b. Prevalence of *Coxiella burnetii* (Legionellales: Coxiellaceae) infection among wildlife species and the tick *Hyalomma lusitanicum* (Acari: Ixodidae) in a Meso-Mediterranean ecosystem. J. Med. Entomol. 57, 551–556.

Guatteo, R., Seegers, H., Taurel, A.-F., Joly, A., Beaudeau, F., 2011. Prevalence of *Coxiella burnetii* infection in domestic ruminants: a critical review. Vet. Microbiol. 149, 1–16.

Gürtler, L., Bauerfeind, U., Blümel, J., Burger, R., Drosten, C., Gröner, A., Heiden, M., Hildebrandt, M., Jansen, B., Offergeld, R., Pauli, G., Seitz, R., Schlenkrich, U., Schottstedt, V., Strobel, J., Willkommen, H., 2014. *Coxiella burnetii* - Pathogenic Agent of Q (Query) Fever. Transfus. Med. Hemotherapy Off. Organ Dtsch. Ges. Transfusionsmedizin Immunhamatologie 41, 60–72. https://doi.org/10.1159/000357107.

Hildebrandt, A., Straube, E., Neubauer, H., Schmoock, G., 2010. *Coxiella burnetii* and Coinfections in *Ixodes ricinus* Ticks in Central Germany. Vector-Borne Zoonotic Dis. 11, 1205–1207. https://doi.org/10.1089/vbz.2010.0180.

Hoover, T.A., Vodkin, M.H., Williams, J.C., 1992. A *Coxiella burnetti* repeated DNA element resembling a bacterial insertion sequence. J. Bacteriol. 174, 5540–5548.

Jiao, J., Zhang, J., He, P., OuYang, X., Yu, Y., Wen, B., Sun, Y., Yuan, Q., Xiong, X., 2021. Identification of Tick-Borne Pathogens and Genotyping of *Coxiella burnetii* in *Rhipicephalus microplus* in Yunnan Province. China. Front. Microbiol. 2718.

Jourdain, E., Duron, O., Barry, S., González-Acuña, D., Sidi-Boumedine, K., 2015. Molecular methods routinely used to detect *Coxiella burnetii* in ticks cross-react with *Coxiella*-like bacteria. Infect. Ecol. Epidemiol. 5, 29230.

Kersh, G.J., Fitzpatrick, K.A., Self, J.S., Priestley, R.A., Kelly, A.J., Lash, R.R., Marsden-Haug, N., Nett, R.J., Bjork, A., Massung, R.F., 2013. Presence and persistence of *Coxiella burnetii* in the environments of goat farms associated with a Q fever outbreak. Appl. Environ. Microbiol. 79, 1697–1703.

Khalili, M., Rezaei, M., Akhtardanesh, B., Abiri, Z., Shahheidaripour, S., 2018. Detection of *Coxiella burnetii* (Gammaproteobacteria: Coxiellaceae) in ticks collected from infested dogs in Kerman, Southeast of Iran. Persian J. Acarol. 7.

Khoo, J.-J., Lim, F.-S., Chen, F., Phoon, W.-H., Khor, C.-S., Pike, B.L., Chang, L.-Y., AbuBakar, S., 2016. *Coxiella* detection in ticks from wildlife and livestock in Malaysia. Vector-Borne Zoonotic Dis 16, 744–751.

Knap, N., Žele, D., Biškup, U.G., Avšič-Županc, T., Vengušt, G., 2019. The prevalence of *Coxiella burnetii* in ticks and animals in Slovenia. BMC Vet. Res. 15, 368.

Knobel, D.L., Maina, A.N., Cutler, S.J., Ogola, E., Feikin, D.R., Junghae, M., Halliday, J. E., Richards, A.L., Breiman, R.F., Cleaveland, S., 2013. *Coxiella burnetii* in humans, domestic ruminants, and ticks in rural western Kenya. Am. J. Trop. Med. Hyg. 88, 513.

Koka, H., Sang, R., Kutima, H.L., Musila, L., 2018. *Coxiella burnetii* Detected in Tick Samples from Pastoral Communities in Kenya. BioMed Res. Int. https://doi.org/10.1155/2018/8158102.

Körner, S., Makert, G.R., Mertens-Scholz, K., Henning, K., Pfeffer, M., Starke, A., Nijhof, A.M., Ulbert, S., 2020. Uptake and fecal excretion of *Coxiella burnetii* by *Ixodes ricinus* and *Dermacentor marginatus* ticks. Parasit. Vectors 13, 1–11.

Körner, S., Makert, G.R., Ulbert, S., Pfeffer, M., Mertens-Scholz, K., 2021. The Prevalence of *Coxiella burnetii* in Hard Ticks in Europe and Their Role in Q Fever Transmission Revisited—A Systematic Review. Front. Vet. Sci. 8.

Kumsa, B., Socolovschi, C., Almeras, L., Raoult, D., Parola, P., 2015. Occurrence and Genotyping of *Coxiella burnetii* in Ixodid Ticks in Oromia. Ethiopia. Am. J. Trop. Med. Hyg. 93, 1074–1081. https://doi.org/10.4269/ajtmh.14-0758.

Lang, G.H., 1990. Coxiellosis (Q fever) in animals. Q Fever 1, 23–48.

Lee, J.-H., Park, H.-S., Jang, W.-J., Koh, S.-E., Park, T.-K., Kang, S.-S., Kim, B.-J., Kook, Y.-H., Park, K.-H., Lee, S.-H., 2004. Identification of the *Coxiella* sp. detected from *Haemaphysalis longicornis* ticks in Korea. Microbiol. Immunol. 48, 125–130.

Leulmi, H., Aouadi, A., Bitam, I., Bessas, A., Benakhla, A., Raoult, D., Parola, P., 2016. Detection of *Bartonella tamiae, Coxiella burnetii* and *rickettsiae* in arthropods and tissues from wild and domestic animals in northeastern Algeria. Parasit. Vectors 9, 27. https://doi.org/10.1186/s13071-016-1316-9.

Machado-Ferreira, E., Vizzoni, V.F., Balsemão-Pires, E., Moerbeck, L., Gazeta, G.S., Piesman, J., Voloch, C.M., Soares, C.A., 2016. *Coxiella* symbionts are widespread into hard ticks. Parasitol. Res. 115, 4691–4699.

Mantovani, A., Benazzi, P., 1953. The isolation of *Coxiella burnetii* from *Rhipicephalus sanguineus* on naturally infected dogs. J. Am. Vet. Med. Assoc. 122, 117–118.

Mediannikov, O., Fenollar, F., Socolovschi, C., Diatta, G., Bassene, H., Molez, J.-F., Sokhna, C., Trape, J.-F., Raoult, D., 2010. *Coxiella burnetii* in humans and ticks in rural Senegal. PLoS Negl Trop Dis 4, e654.

Mtshali, K., Khumalo, Z.T., Nakao, R., Grab, D.J., Sugimoto, C., Thekisoe, O.M., 2015. Molecular detection of zoonotic tick-borne pathogens from ticks collected from ruminants in four South African provinces. J. Vet. Med. Sci. 15–0170.

Muramatsu, Y., Usaki, N., Thongchai, C., Kramomtong, I., Kriengsak, P., Tamura, Y., 2014. Seroepidemiologic survey in Thailand of *Coxiella burnetii* infection in cattle and chickens and presence in ticks attached to dairy cattle. Southeast Asian J. Trop. Med. Public Health 45, 1167.

Ndeereh, D., Muchemi, G., Thaiyah, A., Otiende, M., Angelone-Alasaad, S., Jowers, M.J., 2017. Molecular survey of *Coxiella burnetii* in wildlife and ticks at wildlife–livestock interfaces in Kenya. Exp. Appl. Acarol. 72, 277–289.

Noda, A.A., Rodríguez, I., Miranda, J., Contreras, V., Mattar, S., 2016. First molecular evidence of *Coxiella burnetii* infecting ticks in Cuba. Ticks Tick-Borne Dis 7, 68–70.

Nyaga, V.N., Arbyn, M., Aerts, M., 2014. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch. Public Health 72, 39. https://doi.org/10.1186/2049-3258-72-39.

Ogo, N., de Mera, I.G.F., Okubanjo, O., de la Fuente, J., 2013. Genetic characterization of *Coxiella burnetii* in *Amblyomma varigatum* ticks from North-central Nigeria: public health importance. infection 5, 6.

Pacheco, R.C., Echaide, I.E., Alves, R.N., Beletti, M.E., Nava, S., Labruna, M.B., 2013. *Coxiella burnetii* in ticks. Argentina. Emerg. Infect. Dis. 19, 344.

Philip, C.B., 1948. Observations on Experimental Q Fever. J. Parasitol. 34, 457–464. https://doi.org/10.2307/3273312.

Psaroulaki, A., Chochlakis, D., Angelakis, E., Ioannou, I., Tselentis, Y., 2014. *Coxiella burnetii* in wildlife and ticks in an endemic area. Trans. R. Soc. Trop. Med. Hyg. 108, 625–631.

Reye, A.L., Arinola, O.G., Hübschen, J.M., Muller, C.P., 2012. Pathogen prevalence in ticks collected from the vegetation and livestock in Nigeria. Appl. Environ. Microbiol. 78, 2562–2568.

Reye, A.L., Stegniy, V., Mishaeva, N.P., Velhin, S., Hübschen, J.M., Ignatyev, G., Muller, C.P., 2013. Prevalence of Tick-Borne Pathogens in *Ixodes ricinus* and *Dermacentor reticulatus* Ticks from Different Geographical Locations in Belarus. PLOS ONE 8, e54476. https://doi.org/10.1371/journal.pone.0054476.

Roest, H.I.J., Tilburg, J., Van der Hoek, W., Vellema, P., Van Zijderveld, F.G., Klaassen, C.H.W., Raoult, D., 2011. The Q fever epidemic in The Netherlands: history, onset, response and reflection. Epidemiol. Infect. 139, 1–12.

Ruiz-Fons, F., Ianire, A., Barandika, J., Hurtado, A., Atxaerandio, R., Juste, R., García-Pérez, A., 2010. Seroepidemiological study of Q fever in domestic ruminants in semi-extensive grazing systems. BMC Vet. Res. 6, 3. https://doi.org/10.1186/1746-6148-6-3.

Satta, G., Chisu, V., Cabras, P., Fois, F., Masala, G., 2011. Pathogens and symbionts in ticks: a survey on tick species distribution and presence of tick-transmitted micro-organisms in Sardinia. Italy. J. Med. Microbiol. https://doi.org/10.1099/jmm.0.021543-0.

Seo, M.-G., Lee, S.-H., Ouh, I.-O., Lee, G.H., Goo, Y.-K., Kim, S., Kwon, O.-D., Kwak, D., 2016. Molecular detection and genotyping of Coxiella-like endosymbionts in ticks that infest horses in South Korea. PLoS One 11, e0165784.

Shipman, M., Lubick, K., Fouchard, D., Gurram, R., Grieco, P., Jutila, M., Dratz, E.A., 2013. Proteomic and Systems Biology Analysis of the Monocyte Response to *Coxiella burnetii* Infection. PLOS ONE 8, e69558. https://doi.org/10.1371/journal.pone.0069558.

Siroký, P., Kubelová, M., Modry, D., Erhart, J., Literák, I., Spitalská, E., Kocianová, E., 2010. Tortoise tick *Hyalomma aegyptium* as long term carrier of Q fever agent *Coxiella burnetii*-evidence from experimental infection. Parasitol. Res. 107, 1515–1520. https://doi.org/10.1007/s00436-010-2037-1.

Smith, D.J.W., 1942a. Studies in the epidemiology of q fever 10. The transmission of q fever by the tick ixodes holocyclUS (with notes on tick-paralysis in bandicoots). Aust. J. Exp. Biol. Med. Sci. 20.

Smith, D.J.W., 1942b. Studies in the Epidemiology of Q Fever. 11. Experimental Infection of the Ticks *Haemaphysalis bispinosa* and *Ornithodorus* sp. with *Rickeltsia burneti*. Aust. J. Exp. Biol. Med. Sci. 20.

Smith, D.J.W., Derrick, E.H., 1940. Studies in the Epidemiology of Q Fever. 1. The Isolation of Six Strains of *Rickettsia burneti* from the Tick *Haemaphysalis humerosa*. Aust. J. Exp. Biol. Med. Sci. 18.

Socolovschi, C., Reynaud, P., Kernif, T., Raoult, D., Parola, P., 2012. *Rickettsiae* of spotted fever group, *Borrelia valaisiana*, and *Coxiella burnetii* in ticks on passerine birds and mammals from the Camargue in the south of France. Ticks Tick-Borne Dis. 3, 355–360. https://doi.org/10.1016/j.ttbdis.2012.10.019.

Spitalská, E., Sparagano, O., Stanko, M., Schwarzova, K., Spitalsky, Z., Skultety, L., Havlíková, S., 2018. Diversity of *Coxiella*-like and Francisella -like endosymbionts, and *Rickettsia* spp., *Coxiella burnetii* as pathogens in the tick populations of Slovakia, Central Europe. Ticks Tick-Borne Dis. 9 https://doi.org/10.1016/j.ttbdis.2018.05.002.

Sprong, H., Tijsse-Klasen, E., Langelaar, M., De Bruin, A., Fonville, M., Gassner, F., Takken, W., Van Wieren, S., Nijhof, A., Jongejan, F., 2012. Prevalence of *Coxiella burnetii* in ticks after a large outbreak of Q fever. Zoonoses Public Health 59, 69–75.

Sulyok, K.M., Hornok, S., Abichu, G., Erdélyi, K., Gyuranecz, M., 2014. Identification of Novel *Coxiella burnetii* Genotypes from Ethiopian Ticks. PLOS One 9, e113213. https://doi.org/10.1371/journal.pone.0113213.

Tokarevich, N.K., Panferova, Y.A., Freylikhman, O.A., Blinova, O.V., Medvedev, S.G., Mironov, S.V., Grigoryeva, L.A., Tretyakov, K.A., Dimova, T., Zaharieva, M.M., 2019. *Coxiella burnetii* in ticks and wild birds. Ticks Tick-Borne Dis. 10, 377–385.

Varela Castro, L., Zuddas, C., Ortega, N., SERRANO, E., Salinas, J., Castella, J., Castillo-Contreras, R., Carvalho, J., Lavin, S., Mentaberre, G., 2018. On the possible role of ticks in the eco-epidemiology of *Coxiella burnetii* in a Mediterranean ecosystem. Ticks Tick-Borne Dis 9. https://doi.org/10.1016/j.ttbdis.2018.02.014.

Watanabe, M., Nakao, R., Amin-Babjee, S.M., Maizatul, A.M., Youn, J.H., Qiu, Y., Sugimoto, C., Watanabe, M., 2015. Molecular screening for *Rickettsia, Anaplasmataceae* and *Coxiella burnetii* in *Rhipicephalus sanguineus* ticks from Malaysia. Trop. Biomed. 32, 390–398.

Whiting, P., Rutjes, A.W., Reitsma, J.B., Bossuyt, P.M., Kleijnen, J., 2003. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med. Res. Methodol. 3, 25. https://doi.org/10.1186/1471-2288-3-25.