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Review Article

Prevalence of Bartonella spp. infections in Iran: a systematic review and meta-analysis

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ABSTRACT

Despite the public health importance of Bartonella infections, its epidemiology is under-studied, particularly in Iran. The objective of this systematic review and meta-analysis was to determine the pooled prevalence of Bartonella infections in humans, domestic and wild animals, and invertebrates in Iran, respectively. PubMed, Scopus, Web of Science, Google Scholar, Scientific Information Database (SID), MagIran, and IranDoc databases were searched. Title and abstract screening was done by two independent reviewers based on the eligibility criteria. The eligibility criteria were cross-sectional studies investigating the prevalence of Bartonella infections in humans, pets, farm animals, and parasites in Iran. A random-effects model with Freeman-Tukey Double Arcsine transformation was used for data synthesis. Subgroup analysis was done based on the host species. A total number of 220 results were identified by the search, among which 93 were removed as duplicates. Of the 127 remaining results, 19 studies were included. The molecular prevalence of Bartonella spp. infections was 4% with the highest values observed in rats (17%), dogs (10%) and cats (10%), respectively. The seroprevalence of Bartonella spp. among cat owners and hospital patients in Tehran was 18% and 5%, respectively. Also, the seroprevalence of Bartonella spp. among dogs in Hamadan was estimated to be 74.24%. Based on culture methods, in one study among cats in Shahrekord, 12.5% of blood samples were positive. Based on the findings of the current study, the molecular prevalence of Bartonella spp. in Iran was higher in rats, dogs, and cats. However, more investigations, particularly in other hosts, are recommended.

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1. Context

Bartonella are facultative intracellular bacteria (1), that can infect a wide range of mammalian hosts, including wild and domestic carnivores (2), with some species also associated with human infections, including B. henselae, B. quintana, B. bacilliformis, B. elizabethae, B. vinsonii, B. koehlerae, B. clarridgieae, B. alsatica, B. doshiae, B. grahamii, B. ratti, B. massiliensis, and B. tribocorum (3). Bartonella species have also been isolated froma wide variety of invertebrates , including fleas, ticks, body lice, sheep keds, and even spiders (4).

In humans, Bartonella infections are able to cause relatively mild flu-like symptoms in immunocompetent individuals. However, more severe manifestations have also been cited in immunocompromised patients such as HIV/AIDS patients and organ transplant recipients (3).

Among bartonella spp., B. henselae is the most prevalent zoonotic species with a global distribution and is the causative agent of Cat-Scratch Disease. Infections with B. henselae in immunocompromised patients, predisposes the patient to bacillary angiomatosis and peliosis hepatis (5, 6). Moreover, B. henselae has been considered the most common cause of neuritis often followed by acute loss of vision (7). In addition to B. henselae, B. quintana, the etiological agent of trench fever, can also cause bacillary angiomatosis and peliosis hepatis in HIV patients, chronic bacteremia, chronic lymphadenopathy, and blood culture negative endocarditis (8).

The transmission mode of Bartonella spp. to humans is caused by the scratches from an infected reservoir host or via contact with the infectious faeces of arthropod vectors such as fleas (9). Bartonella spp. are considered neglected zoonotic pathogens (10). Despite its public health importance, the epidemiology of Bartonella spp. remains under-studied (11), particularly in Iran, where- despite being isolated from cats, dogs, ticks, fleas, and humans in some studies (12-14), no systematic review and meta-analysis has been carried out. Therefore, the aim of this systematic review was to summarize and estimate the pooled prevalence of Bartonella infections in humans, domestic and wild animals, and invertebrates in Iran.

2. Data Acquisition

This systematic review and meta-analysis study was prepared and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline (15).

2.1. Search strategy

PubMed, Scopus, Web of Science, Google Scholar, Scientific Information Database (SID), MagIran, and IranDoc were searched on 03 October, 2023 with "Bartonella" OR "bartonellosis" OR "Cat scratch disease" AND "Iran". Search was carried out according to the settings of each database with no restrictions on publication date. For PubMed, Scopus, and Web of Science only English keywords were used whilst for Google Scholar, SID, and MagIran both English and the Persian translation of the keywords were used. All results were extracted, except for Google Scholar, where all results found using Persian keywords and the first 100 results found using English keywords were extracted. The results were gathered in an EndNote library. Only one copy of the duplicate results were kept.

2.2. Title and abstract screening

The titles and abstracts of the results were screened by two independent reviewers in order to identify eligible papers based on the inclusion/exclusion criteria. The inclusion criteria were cross-sectional studies investigating the prevalence of Bartonella infections in humans, pets, farm animals, and parasites in Iran. Conflicts arising over the eligibility of the papers were solved by discussion.

2.3. Data extraction

The last name of the first author, year of publication, sampling period, genus of Bartonella isolates, type of utilized diagnostic test, number of positive infections, sample size, species of the host, and sampling location were extracted into an Excel file.

2.4. Statistical analysis

For meta-analysis, a random-effects model was used and Freeman-Tukey Double Arcsine transformation was applied to stabilize the variance. If a study had pooled biological samples, the pooled point estimate was used. Initially, it was planned to perform the meta-analysis for each detection method separately. However, the meta-analyses of the seroprevalence and culture-based prevalence were not carried out due to the low number of studies using the mentioned detection methods. Instead, the findings of these detection tests were summarized narratively. Subgroup analysis was performed for the species of the hosts. All of the statistical analysis were performed using Stata version 17.

3. Results

A total number of 220 results were identified. 93 results were deleted as duplicates. The titles and abstracts of 127 results were screened, and initially, 22 papers were deemed eligible, full-texts were subsequently sought for these. However, the study by Saydam et al. (16) was excluded because when the corresponding author was contacted, it was revealed that the study only enrolled confirmed cases of bartonellosis and prevalence could not be determined. A conference paper by Sazmand et al. (17) was deemed duplicate and excluded due to the similarity of the authors, the location of sampling, and sample size with another study that was already included. A conference paper by Greco (18) was excluded because the corresponding author did not provide the full-text. Finally, 19 papers were included (Figure 1). The characteristics of the included studies are presented in Table 1.

3.1. Detection tests

Polymerase Chain Reaction (PCR) was the most frequently-used detection test (n=18), while Indirect Immunofluorescent Antibody Assay (IFA) and culture were each applied in two studies.

3.2. Host range

The DNA of Bartonella spp. has been isolated from Norway rats (1 study), camels (1 study), cats (5 studies), dogs (3 studies), *Ctenocephalides canis* and *Pulex Irritans* fleas (1 study), and *Rhipicephalus sanguineus* ticks (1 study). Also, the sero-positivity for Bartonella spp. has been detected in humans (1 study).

3.3. Molecular prevalence of Bartonella spp.

Based on PCR methods, the pooled prevalence estimate of Bartonella spp. infection was 4% (95% CI: 2-8%), withan I^2 value of 93.89%. In subgroup analysis, the highest prevalence of Bartonella infections was observed in dogs (10%, 95% CI: 1-25%) and cats (10%, 95% CI: 7-13%). For the subgroups of dogs and cats, the I^2 value was 92.93% and 0%, respectively. The pooled estimate of Bartonella spp. infection prevalence in rats, camels, ticks, fleas, and humans were 17%, 3%, 0%, 0%, and 0%, respectively (Figure 2).

3.4. Seroprevalence of Bartonella spp.

Among humans, the seroprevalence of Bartonella spp. was 18% among cat owners and 5% in hospital patients in Tehran. Among 66 dogs in Hamadan, the sero-prevalence was 74.24%.

3.5. Culture prevalence of Bartonella spp.

In one study involving 40 cats in Shahrekord, five culture-positive blood samples (12.5%) were obtained, while no culture-positive nail samples (0%) were detected, and two saliva samples were considered suspected. The culture-positive blood samples were validated by PCR; however, the PCR method did not confirm the suspected saliva samples. Additionally, in one study involving 100 cats in Tehran, no culture-positive blood samples were obtained.

This systematic review and meta-analysis aimed to estimate the pooled prevalence of Bartonella spp. infections in humans, domestic and wild animals, and invertebrates in Iran.

Based on the findings of this study, the overall pooled estimate of Bartonella infections detected by PCR methods in Iran was 4% (95% CI: 2-8%). It is worth mentioning that the pooled prevalence of Bartonella infections was higher in cats (10%) and dogs (10%) compared to humans, camels, rats, ticks, and fleas. The pooled prevalence of Bartonella spp. infection in dogs in the present study was lower than the global pooled estimate of 15.03%. Furthermore , the molecular prevalence of Bartonella spp. infection in cats in this study was higher than the global pooled estimate of 3.6% (2). However, based on culture-based methods, the prevalence of Bartonella spp. in cats was 12.5% in Shahrekord and 0% in Tehran (19, 20). The domestic cat is not only the definitive host for *Toxoplasma gondii* (21), but also serves as the primary reservoir for B. henselae, B. clarridgeiae, and B. koehlerae (22), with the potential to act as subclinical carriers of Bartonella spp. (23). All Bartonella spp. identified in sick dogs, such as B. clarridgeiae and B. washoensis, are known to be pathogenic or potentially pathogenic to humans, suggesting that dogs may serve as valuable sentinel species and comparative models for human Bartonella infections (10). The degree of hygiene compliance among dog owners and handlers following exposure to dogs, the level of intimacy between dogs and their owners and children, and the adequacy of management practices among dog owners and handlers may contribute to the risk of zoonotic canine parasitic infections in humans (24).

The molecular prevalence of Bartonella spp. in Norway rats (17%) in Iran was higher than Chile. In Chile, 43 (27.7%) out of 155 spleen samples and six out of 50 blood samples (12%) from rodents were identified as positive for Bartonella spp. (25). More than 20 species of Bartonella have been isolated from wild rodents. Rodents along with bats, are known to harbor the highest diversity

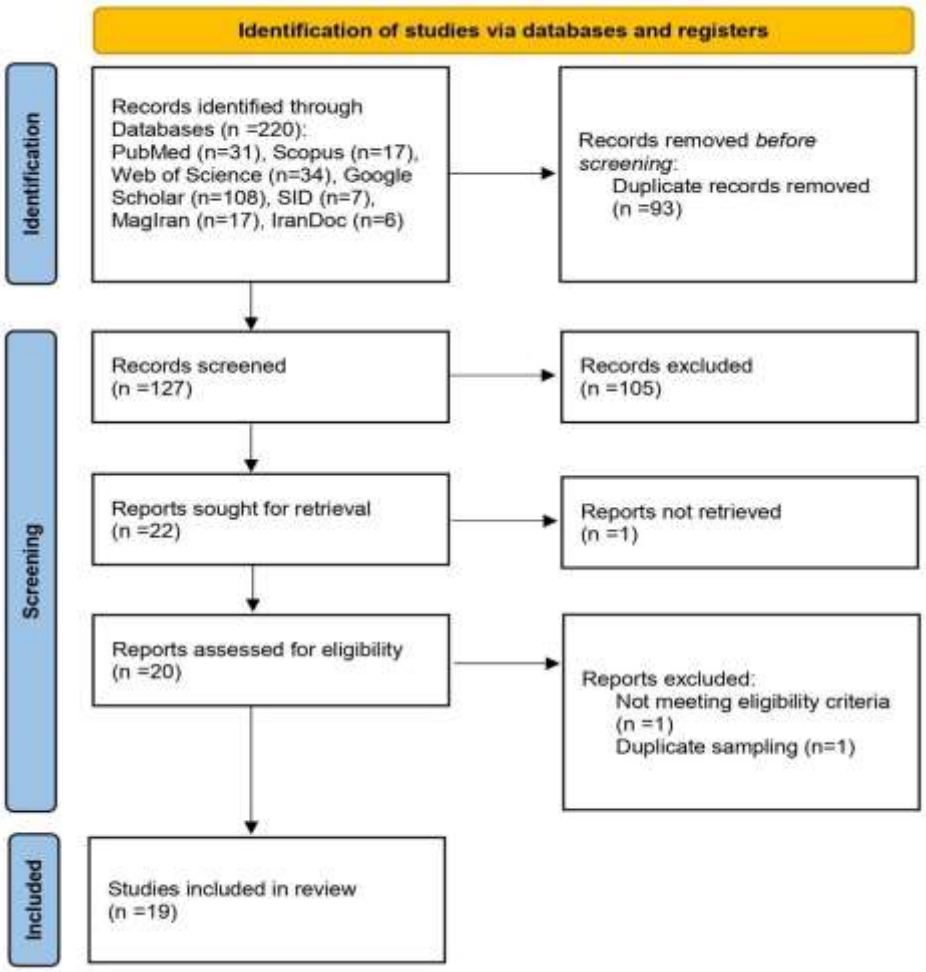

Figure 1. Flow chart of the studies.

Table 1. The summary of the characteristics of the included studies.

	Author	Publication year	Sampling period	Bartonella species	Test	Biological sample	Number of positive	Sample size	host	Location
1	Azimi (37)	2021	May 2018 - December 2019	Bartonella spp.	PCR	Fecal DNA	17	100	Norway Rats (*Rattus norvegicus*)	Tehran
2	Bahari (38)	2021	January 2018- June 2018	Bartonella spp.	PCR	Jugular vein blood, brain, liver, portal lymph node	0	100	Camels (*Camelus dromedarius*)	Qom
3	Dirbazian (39)	2022	-	Bartonella quintana	PCR	Culture-negative endocarditis specimens	0	60	Humans from selected military hospitals	-
4	Gaemi (40)	2019	-	Bartonella spp.	PCR	Blood	18	106	Camels (*Camelus dromedarius*)	Fars
5	Ghasemi (41)	2022	2017-2018	Bartonella spp.	PCR	Pooled ticks	0	638	Ticks (Ixodes, Haemaphysalis, Hyalomma, and Rhipicephalus spp.)	Golestan, Mazandaran, and Guilan
6	Greco (42)	2019	October 2018	Bartonella henselae, Bartonella clarridgeiae, and Bartonella vinsonii subsp. berkhoffii.	PCR, Indirect immunofluorescent antibody assay	Blood	49 seropositive, 16 PCR positive	66 rescued stray dogs and dogs in dog-breeding facility	Dogs	Hamadan
7	Jajarmi (43)	2022	July-September 2022	Bartonella henselae	Nested-PCR	Blood	4	72	Cats	Kerman city
8	Mazaheri Nezhad Fard (44)	2016	January- April 2012	Bartonella henselae	PCR	Nail, saliva	5 nail samples, 1 saliva sample	70 (70 nail, 70 saliva)	Cats	Tehran

9	Mirzadeh (45)	2015	August 2012-October 2014	Bartonella spp.	PCR	Flea	0	190	Fleas (*Pulex Irritans*)	Khodabande and Mahneshan, Zanjan
10	Oskouizadeh (19)	2008	2005	Bartonella henselae	Culture, Indirect immunofluorescent antibody	Blood	0 from culture, 23 seropositive 18 seropositive, 5 seropositive	100 cats 100 pet owners 100 human patients in hospital	Cats, Humans	Tehran
11	Oskouizadeh (46)	2010	June 2005-November 2007	Bartonella henselae	PCR	Jugular vein blood, nail, saliva	12 saliva positive, 0 blood positive, 0 nail positive 0 saliva positive, 5 blood positive, 0 nail positive	110 pet cats 30 stray cats	Cats	Shahrekord, tehran
12	Oskouizadeh (20)	2011	-	Bartonella henselae	Culture, PCR	Jugular vein blood, nail, saliva	0 blood positive, 0 saliva positive, 0 nail positive 5 blood positive, 2 saliva positive, 0 nail positive	10 pet cats 30 stray cats	Cats	Shahrekord
13	Oskouizadeh (47)	2013	-	Bartonella henselae	PCR	Cephalic vein blood, saliva, nail	0 blood positive, 0 saliva positive, 0 nail positive	100	Dogs	Ahvaz
14	Samsami (48)	2020	-	Bartonella spp.	PCR	Cephalic vein blood	12	98	Dogs	Fars
15	Sazmand (49)	2019	June- July 2014	Bartonella spp.	PCR	Blood	0	200	Camels (*Camelus dromedarius*)	central and south-eastern Iran
16	Seidi (13)	2021	April 2018-May 2019	Bartonella spp.	PCR	Flea	10	1937	Fleas (*Ctenocephalides canis*, *Pulex Irritans*)	Kermanshah, Kurdistan, West Azerbaijan, Hamadan, and Lorestan
17	Shamshiri (32)	2023	September 2018- January 2020	Bartonella spp.	PCR	Cephalic vein blood, fleas, ticks	14 0 1	100 dogs 31fleas 12 ticks	Dogs, Fleas (*Ctenocephalides canis*, *Pulex Irritans*), Ticks (*Rhipicephalus sanguineus*)	Hamadan, Kermanshah
18	Shamshiri (23)	2022	December 2018-February 2021	Bartonella spp.	PCR	Cephalic or saphenous vein blood	11	87	Cats	Hamadan, Kermanshah
19	Zurita (50)	2016	-	Bartonella spp.	PCR	Flea	0	7	Fleas (*Ctenocephalides felis*)	Nashtarood, Mazandaran

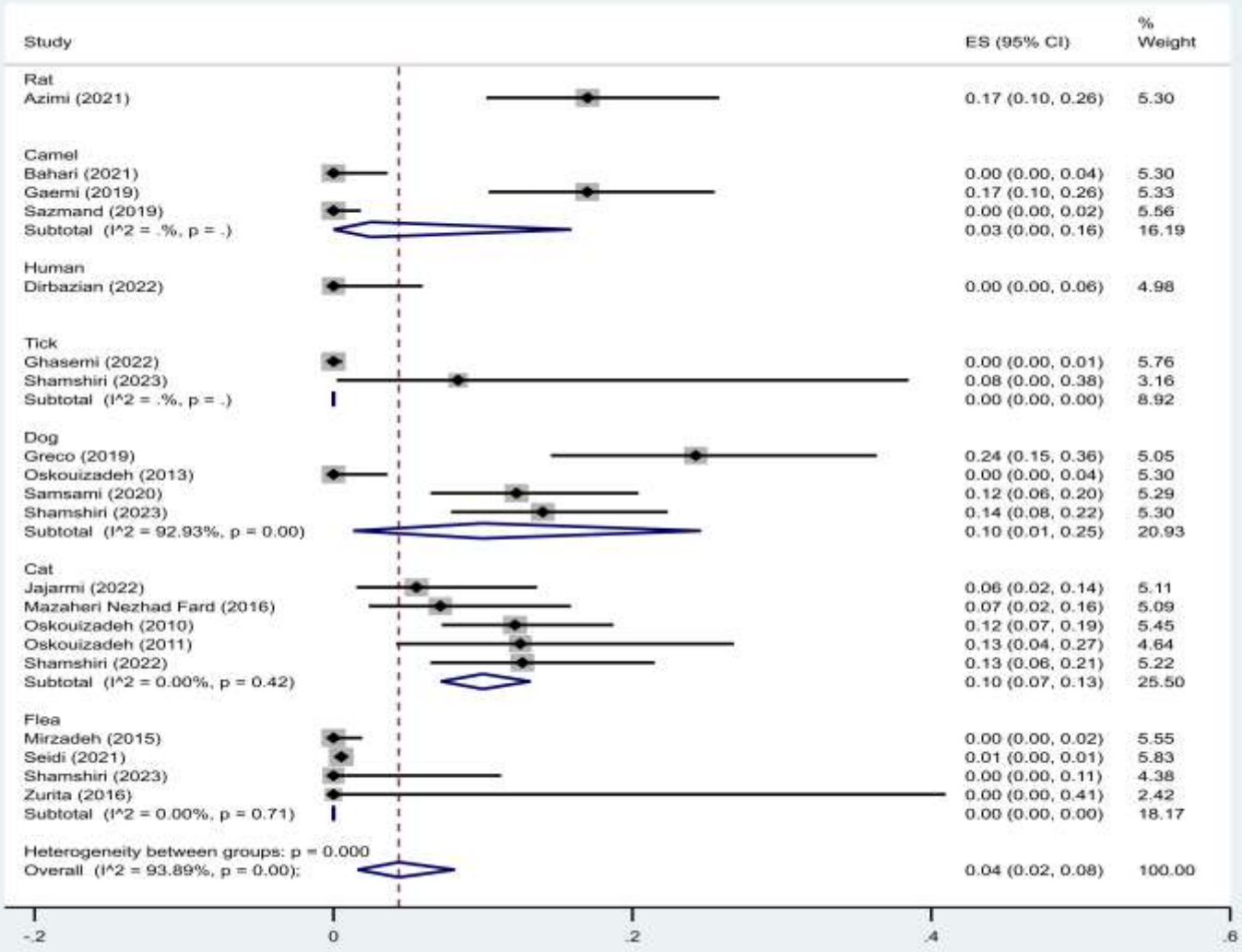

Figure 2. Pooled estimate and subgroup analysis of molecular prevalence of Bartonella spp. infections in Iran.

of Bartonella spp., with several rodent-adapted strains capable of infecting humans (26). Due to the close association with humans in urban environments, Norway rats play an important role in the transmission of zoonotic diseases to humans (27).

In the present study, based on a previous research, the prevalence of B. quintana in Iranian culture-negative endocarditis specimens from military hospitals, as determined by PCR, was zero (28). B, quintana is transmitted by lice in environments with poor hygiens (8). Homeless people have been considered the main target of B. quintana, with the period of homelessness, age, and alcoholism being associated with susceptibility to infection (29).

In this study, the seroprevalence of Bartonella spp. among humans was 18% among cat owners and 5% among patients in a hospital in Tehran (19). This finding was lower compared to data from Egypt, where the prevalence of B. henselae infection among cat owners and individuals with a history of contact with cats was estimated at 51.4% and 42.9%, respectively (30).

In the present study, the pooled prevalence of Bartonella spp. in camels was 3% (95% CI: 0-16%). This result is consistent with the findings of Selmi et al. (31), who reported the prevalence of Bartonella spp. and B. henselae by PCR in camels in Tunisia as 3.6% and 3.1%, respectively (31).

In the present study, the pooled prevalence of Bartonella spp. in fleas was nearly zero. In one included study,

Bartonella spp. was detected by PCR in 10 out of 1,937 *Ctenocephalides canis* and *Pulex Irritans* fleas (13). Fleas such as *Ctenocephalides felis* are known to play a significant role in transmission of Bartonella spp., which are capable of multiplying within the flea digestive tract (2). However, given the nearly zero prevalence in this study, fleas seem to play a minimal role in the transmission of Bartonella spp. in Iran.

In the present study, the pooled prevalence of Bartonella spp. in ticks was nearly zero. In one included study, Bartonella spp. was detected by PCR in 1 out of 12 *Rhipicephalus sanguineus* that were collected from dogs (32). Our pooled estimate is lower compared to findings from Thailand and Malaysia, where the molecular prevalence of Bartonella spp. in ticks was estimated at 2.5% and 5.26%, respectively (33, 34).

In this systematic review, no studies were identified involving other animal species, including wildlife animals, domestic animals such as sheep and cattle, or ectoparasites such as lice. The primary limitation of the individual studies included in this systematic review and meta-analysis was the limited number of studies, particularly those involving humans, rodents, and other animal species. Therefore, further investigations on Bartonella spp. infections in Iran are recommended.

Bartonella infections are diseases of both medical and veterinary importance. Thus, the One Health approach should be applied to collect more data and implement appropriate preventive and control measures (2, 35), by linking medicine, veterinary medicine, farming, and the economic sectors to improve public health outcomes (36).

4. Conclusion

In conclusion, based on the findings of this study, the overall molecular prevalence of Bartonella spp. infections was 4% (95% CI: 2-8%), with the highest values observed in rats [17% (95% CI: 10-26%)], dogs [10% (95% CI: 1-25%)], and cats [10% (95% CI: 7-13%)]. Moreover, the pooled molecular prevalence in camels, humans, ticks, and fleas were 3% (95% CI: 0-16%), 0%, near zero, and near zero, respectively. Among studies utilizing serological methods, in one study among humans, the seroprevalence of Bartonella spp. was 18% among cat owners and 5% among hospital patients in Tehran. Among dogs in Hamadan, the sero-prevalence of Bartonella spp. was estimated to be 74.24%. Moreover, based on culture methods, in one study among cats in Shahrekord, five culture-positive blood samples were reported (12.5%) and, in another study among cats in Tehran, the prevalence was zero. Further investigations on Bartonella spp. infections in Iran, particularly among under-studied hosts, are recommended.

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Authors' Contribution

Study concept and design: A. FD, M. S.
Acquisition of data: A. FD, M. S.
Analysis and interpretation of data: A. FD, P. K.
Drafting of the manuscript: A. FD, H. A.
Critical revision of the manuscript for important intellectual content: A. FD.
Statistical analysis: A. FD, H. A.
Administrative, technical, and material support: A. FD, P. K, H. A, M. S.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare no conflict of interest.

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Data Availability

Datasets and statistical codes are available upon request from the authors.

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