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

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 study 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. And, the title and abstracts 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 due to being duplicates. Out 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). While, the sero-prevalence of Bartonella spp. among cat owners and hospital patients in Tehran was 18% and 5%, respectively. And, the sero-prevalence 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 our findings, the molecular prevalence of Bartonella spp. in Iran was higher in rats, dogs, and cats. However, more investigations particularly in other hosts is recommended.

Keywords: Bartonella, Bartonella infections, Systematic review, Iran

1. Context

The genus Bartonella are facultative intracellular bacteria (1) that are able to infect a vast range of mammalians, including wild and domestic carnivores (2) with some species also associated with infection among humans 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 from a vast number 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. But, 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 global distribution and is the causative agent of Cat-Scratch Disease. Moreover, 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). Whilst, B. quintana, the etiological agent of trench fever, is also able to 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 by 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). And, despite its public health importance, epidemiology of Bartonella spp. is yet under-studied (11). Particularly in Iran, where in spite of its 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 publication time limit. 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 of the results were extracted except for Google Scholar, in which, all of the results found with the Persian keywords and the first 100 results found with the 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 was cross-sectional studies investigating the prevalence of Bartonella infections in humans, pets, farm animals, and parasites in Iran. Conflicts risen upon the eligibility of the papers were solved by discussion.

2.3. Data extraction

The last name of the first author, the year of publication, the sampling period, the genus of Bartonella isolates, the type of utilized diagnostic test, the number of positive infections, number of sample size, the species of the host, and the location of sampling 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. But, the meta-analyses of the sero-prevalence and culture-based prevalence were not carried out due to the low number of studies utilizing 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 with Stata version 17.

3. Results

A total number of 220 results were identified. 93 results were deleted due to be being duplicates. The title and abstracts of 127 results were screened and initially, 22 papers were deemed eligible for which the full-texts were sought. 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.

Insert Figure 1

Insert Table 1

3.1. Detection tests

Polymerase Chain Reaction (PCR) methods were the most frequently-used detection test (n=18) and Indirect immunofluorescent antibody assay (IFA) was used in two studies and culture was applied in two studies.

3.2. Host range

The DNA of Bartonella spp. have 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). And, 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 estimate of the prevalence of infection with Bartonella spp. was 4% (95% CI: 2-8%) and the I-squared was 93.89%. In subgroup analysis, the 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-squared was 92.93% and 0%, respectively. The pooled estimate of prevalence of Bartonella spp. in rats, camels, ticks, and fleas, and humans were 17%, 3%, 0%, 0%, and 0%, respectively (Figure 2).

Insert Figure 2

3.4. Sero-prevalence of Bartonella spp.

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

3.5. Culture prevalence of Bartonella spp.

In one study among 40 cats in Shahrekord, five culture-positive blood samples (12.5%), zero culture-positive nail samples (0%) and two suspected saliva samples were obtained. The culture-positive blood samples were validated by PCR. But, the PCR method did not validate the suspected saliva samples. And, in one study among 100 cats in Tehran, no culture-positive blood samples were obtained.

The aim of this systematic review and meta-analysis study was to estimate the pooled prevalence of Bartonella spp. infections in humans, domestic and wild animals, and invertebrates in Iran.

Based on our findings, the overall pooled estimate of Bartonella infections based on PCR methods in Iran was 4% (95% CI: 2-8%). And, the pooled prevalence 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 (15.03%). And, the molecular prevalence in cats was higher than the global pooled estimate (3.6%) (2). However, by culture-based methods, the prevalence of Bartonella spp. in cats in Shahrekord and Tehran were 12.5% and zero, respectively (19, 20). The domestic cat is not only the definite host for *Toxoplasma gondii* (21) but also serves as the primary reservoir for B. henselae, B. clarridgeiae, and B. koehlerae (22) with the possibility of being subclinical carriers of Bartonella spp. (23). Whilst all Bartonella spp. identified in sick dogs such as B. clarridgeiae and B. washoensis are known as pathogenic or potentially pathogenic for humans, suggesting that dogs may act as beneficial sentinel species and comparative models for human infections (10). The extent of compliance with hygiene measures amongst dog

owners and handlers following exposure to dogs, the extent of intimacy between dogs and their owners along with their children, and the extent of the management measures of dog owners and handlers might be predisposing to the likelihood of zoonotic canine parasitic infections in humans (24).

The molecular prevalence of Bartonella spp. in Norway rats (17%) in Iran was higher than Chile where 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 Bartonella species have been isolated in wild rodents. Moreover, rodents alongside bats have been known to possess the highest levels of diversity of Bartonella spp. with some rodent-adapted species able to infect humans (26). Due to the close contact with humans in urban settings, Norway rats play an important role in the transmission of zoonotic diseases to humans (27).

In the present study, based on one study, the prevalence of B. quintana in Iranian culture-negative endocarditis specimens from military hospitals by PCR was zero (28). B, quintana is transmitted by lice under poor hygienic conditions (8). Homeless people have been considered the main target of B. quintana, with the period of homeless, age, and alcoholism being associated with the susceptibility to infection (29). In our study, the sero-prevalence of Bartonella spp. among humans was 18% amongst cat owners and 5% in patients in a hospital in Tehran (19). This finding was lower in comparison with the findings in Egypt where B. henselae infection amongst cat owners and individuals with a history of contact with cats were estimated to be 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 is consistent with the finding of Selmi et al. who determined 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 near zero. In one included study, Bartonella spp. was detected by PCR in 10 out of 1937 *Ctenocephalides canis* and *Pulex Irritans* fleas (13). Fleas such as *Ctenocephalides felis* have been known to have a significant role in transmitting Bartonella spp. and Bartonella spp. are able to multiply in flea stomachs (2). However, due to its near zero prevalence in our study, it seems that fleas do not play a major role in the transmission of Bartonella spp. in Iran.

In the present study, the pooled prevalence of Bartonella spp. in ticks was near 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 in comparison with the findings in Thailand and Malaysia where the molecular prevalence of Bartonella spp. in ticks were estimated to be 2.5% and 5.26% (33, 34).

In this systematic search, no studies were identified for other animal species including wildlife animals, domestic animal such as sheep and cattle, and ecto-parasites such as lice. The limitations of the individual studies included in this systematic review and meta-analysis were the low number of conducted studies particularly in humans and rodents and other species. Therefore, conducting more investigations on Bartonella spp. infections in Iran is recommended.

Bartonella infections are diseases of both medical and veterinary importance. Thus, the One Health approach must be applied in order to collect more data and to implement proper preventive and control measures under the One Health approach (2, 35) and by linking medicine, veterinary medicine, farming, and the economy sectors in order to enhance the status of the health of human populations (36).

4. Conclusion

In conclusion, based on our findings, the overall, molecular prevalence of Bartonella spp. infections was 4% (95% CI: 2-8%) with the highest values in rats 17% (95% CI: 10-26%), dogs 10% (95% CI: 1-25%) and cats 10% (95% CI: 7-13%). And, the pooled molecular prevalence in camels, humans, ticks, and fleas were 3% (95% CI: 0-16%), 0%, near 0%, and near 0%, respectively. Among studies utilizing serology methods, in one study among humans, the sero-prevalence of Bartonella spp. was 18% among cat owners and 5% among hospital patients in Tehran. And, among dogs in Hamadan, the sero-prevalence was estimated to be 74.24%. And, based on culture methods, in one study among cats in Shahrekord, five culture-positive blood samples (12.5%). And, in one study among cats in Tehran, the prevalence was zero. More investigations on Bartonella spp. infections in Iran in particular in other hosts is suggested.

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Not Applicable.

Author Contribution

Conceptualization: A.FD, M.S; Protocol design: A.FD, H.A; Search: A.FD; Abstract screening: A.FD, P.K. Data extraction: A.FD; Statistical analysis: A.FD, H.A; Writing first draft: A.FD, P.K; Review and edit: H.A, M.S.

Conflict of Interest

The authors declare no conflict of interest.

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Protocol information

The protocol of this systematic review and meta-analysis was not registered in the registries of systematic review protocols. The protocol is provided in the Data Acquisition section.

Data availability

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

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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, Hyalom	Golestan, Mazandaran, and Guilan

									ma, and Rhipicephalus spp.)	
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	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	100 cats	Cats, Humans	Tehran
							18 seropositive,	100 pet owners		
							5 seropositive	100 human patients in hospital		
11	Oskouizadeh (45)	2010	June 2005-November 2007	Bartonella henselae	PCR	Jugular vein blood, nail, saliva	12 saliva positive, 0 blood positive, 0 nail positive	110 pet cats	Cats	Shahrekord, tehran
							0 saliva positive, 5 blood positive, 0 nail positive	30 stray cats		
12	Oskouizadeh (20)	2011	-	Bartonella henselae	Culture, PCR	Jugular vein blood, nail, saliva	0 blood positive, 0 saliva positive, 0 nail positive	10 pet cats	Cats	Shahrekord
							5 blood positive,	30 stray		

							2 saliva positive, 0 nail positive	cats		
13	Oskouizadeh (46)	2013	-	Bartonella henselae	PCR	Cephalic vein blood, saliva, nail	0 blood positive, 0 saliva positive, 0 nail positive	100	Dogs	Ahvaz
14	Samsami (47)	2020	-	Bartonella spp.	PCR	Cephalic vein blood	12	98	Dogs	Fars
15	Sazmand (48)	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 (49)	2016	-	Bartonella spp.	PCR	Flea	0	7	Fleas (*Ctenocephalides felis*)	Nashtarood, Mazandaran

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٣٤٢ *Figure 1. Flow chart of the studies.*

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

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