REVIEW ARTICLE

Epidemiology of Q fever in Iran: A systematic review and meta-analysis for estimating serological and molecular prevalence

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Background: Q fever is endemic in Iran, thus, we conducted a systematic review and meta-analysis on epidemiology of *Coxiella burnetii* among humans and animals in Iran. **Materials and Methods:** A systematic search was performed to identify all articles reporting *C. burnetii* prevalence in Iranian humans or animals, published from January 2000 to January 2015. Data from articles were extracted, and a pooled estimate of prevalence with corresponding 95% confidence interval (CI) was calculated using random effect method. **Results:** In this review, 27 papers were identified. The pooled seroprevalence of Q fever in animals was 27% (CI 95%: 23%–32%). The prevalence was 33% (CI 95%: 22%–45%) in goats, 27% (CI 95%: 21%–32%) in sheep, and 17% (CI 95%: 5%–28%) in cattle. The bacterial DNA was detected in 5% (95% CI: 3%–9%) of milk samples, and it was higher in cattle (10%; 95% CI: 6%–16%) than sheep (2%; 95% CI: 0–7%) and goats (4%; 95% CI: 0–12%). **Conclusion:** *C. burnetii* DNA or its antibody has been frequently detected among ruminants. Since these animals can transmit the infection to humans, Q fever could be a potential health problem in Iran.

Key words: Iran, meta-analysis, molecular, Q fever, serology

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INTRODUCTION

Q fever is a zoonotic disease caused by *Coxiella burnetii*, a small, obligate, intracellular, Gram negative bacterium. The disease has a worldwide distribution except in New Zealand and Antarctica.[1]

Cattle, sheep, and goats are the primary reservoirs for human infection. However, this bacterial species can infect many animal species.[2] Infections classically occur through inhalation of contaminated aerosols directly from birth fluids of infected animals. However, the consumption of milk and dairy products, skin contact, and person-to-person transmission is other routes of transmission of the infection.[3]

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In humans, *C. burnetii* infection is associated with a wide range of clinical manifestations from asymptomatic to fatal disease.[4,5] The most common clinical sign in acute Q fever is an influenza-like illness, but pneumonia and/or hepatitis might also occur. In the chronic form, the main clinical manifestation is endocarditis.[5,6]

C. burnetii displays two antigenic phases, Phase I and Phase II. In acute infection, the Phase II IgG antibody titer is raised and is higher than the Phase I IgG antibody titer, whereas in chronic infection the Phase I IgG titer is also raised and it might be higher than the Phase II IgG titer.

C. burnetii is resistant to physical stresses and can survive for years in the environment in a spore-like form. The

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bacteria can travel long distances as an aerosol and may be have an important role in disease transmission.[7]

Like other countries in the Middle East, Q fever is endemic in Iran.[7] In recent years, there is an increased interest on the research and diagnosis of Q fever in Iran. However, no nationwide study is performed to assess the seroprevalence of this disease in the country. We performed a systematic review and meta-analysis of the published literature on the Q fever in Iran to amalgamate knowledge and to identify the knowledge gaps about this infection in animals and humans. This study also determines the future research priorities.

MATERIALS AND METHODS

Search strategy and inclusion criteria

We searched the databases PubMed, ISI web of sciences, and Scopus as the main international database and Iranmedex, Magiran, Scientific Information Database and Irandoc for Persian-language articles. These national databases cover Iranian scientific journals, and they have systematic search potential.

The search strategy was based on the terms "Q fever," "*Coxiella burnetii*," and "Iran" in English sources. For national databases, we used both English and Persian keywords. The database search was performed from the year 2000 to January 15, 2015, to obtain the articles that assessed the prevalence of Q fever infection in human and animals in Iran. We searched from the year 2000 because an increased interest has been seen in Q fever research in Iran since this year. All articles reporting *C. burnetii* prevalence in humans or animals by every serological or molecular method were included in the study.

Article selection was performed through 2 levels of study screening. A primary screening for titles and abstracts of the reports was independently done by two investigators (ZN, SH) to exclude irrelevant articles. The basic science, reviews/editorials, letters, comments, case reports, and *in vitro* studies were excluded from the study. We reviewed full texts of included articles and exclude redundant articles. Cases of disagreement were resolved through discussion. If consensus was not achieved, articles were assessed by the corresponding author (A. B.), who was a specialist in infectious diseases. The reference lists of the articles were reviewed to identify more reports, which could be included in the meta-analysis.

Quality assessment

Quality of the relevant studies was evaluated by a scoring system through a modified checklist by two independent reviewers (ZN, SH).[8,9] Items of the target population, sampling methods, sample size, detailed description of methods, sufficient coverage of the sample, data analysis, objective and standard criteria, reliability of results, reporting confounding factors, and subpopulations were assessed. Items were rated as unclear (score = 1), negative response (score = 2) and positive response (score = 3), and the sum of the items was the final quality score.[8] The final score ranged from 10 (if all items were rated as "unclear") to 30 (if all were rated as "positive response").

Data extraction

For all included articles, data were extracted according to the city or region, year of study, sample size, number of studied herds, sampling method, the species (goats, cattle, sheep, tick, humans, camels, dogs), diagnostic test, gene for molecular studies, number of *C. burnetii* positive samples, and flock-level prevalence. In the case of deficient data or unknown methods, authors were contacted for further information.

Data analysis

Pooled estimates of the prevalence of Q fever were estimated using random-effects meta-analysis. This allows a more robust and reliable estimate of prevalence and one that is weighted by the sample size of individual studies. A random effects model weighs studies more equally and is considered more appropriate for meta-analyses with substantial heterogeneity. The between-study variance or heterogeneity in estimated prevalence was evaluated using Cochran Q and the I^2 statistic. The Q statistic is reported with Chi-square and P values and the I^2 statistic is reported as a percentage with increasing values indicating greater heterogeneity between estimates of individual studies ($I^2 < 25\%$ indicates low heterogeneity; 30%–70% = moderate heterogeneity; and >75% indicates high heterogeneity. Publication bias was graphically assessed using funnel plot and Egger's test. For covering the heterogeneity, we also conducted subgroup analysis; in serological context, the considered subgroups were based on animal type and sex and in molecular context subgroups were based on animal type and gene.

RESULTS

A total of 139 papers were identified after duplicates were removed 75 articles remained. Finally, 33 studies were accepted after the title and abstract review. Six articles were excluded due to redundancy. Finally, 27 studies were included in the systematic review.[10-36] Articles were divided into serological[10-21,35] and molecular studies.[22-34,36] The reasons for including or excluding the studies are categorized and reported in Figure 1.

Serological studies

Overall, 13 papers of serological studies were identified, which measured antibodies to *C. burnetii* in blood or milk. All of these

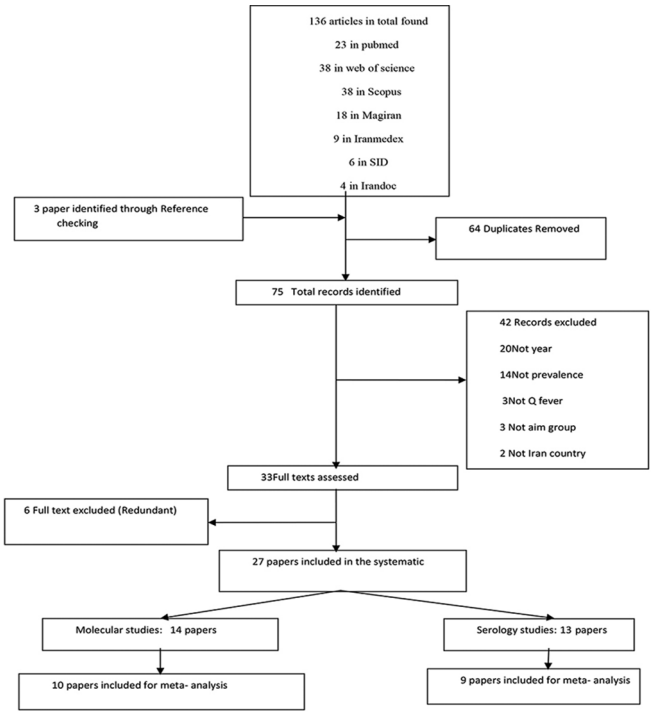

Figure 1: Diagram of systematic review for Q fever infection prevalence in IR Iran

studies used ELISA assay to detect antibodies. In only one study, bulk tank milk samples were tested for antibodies against C. *burnetii* and a prevalence of 45.4% was seen in the herds.[35] In three surveys, antibodies were tested in blood samples from humans; Khalili *et al*. found that 68% of slaughterhouse workers were IgG II seropositive in the southeast of Iran.[20] The second article, from western of Iran, reported IgG antibodies against C. *burnetii* in 27.83% of high-risk population (Hunters, butchers, and health-care workers) and controls.[19] In another survey, IgM antibody was assessed in slaughterhouse workers and 7.8% were positive.[21] Those four articles were not included in meta-analysis due to the lack of adequate data for pooling. Hence, nine studies were included in our meta-analysis which all of them examined antibodies in ruminants' blood.[10-18]

Overall, 3334 cases (339 cattle, 2293 sheep, and 702 goats) were included, of which 828 (65 cattle, 549 Sheep, and 214 goats) were positive. The quality scores of the relevant articles ranged from 12 to 24.

The sample size was different in included papers, with the largest having a sample size of 1280 and the smallest with over 80.[14,18] Five studies predicted the sex-specific seroprevalence, which we used in our meta-analysis.[13-17] Characteristics of the considered studies are available in Table 1.

The range of the Q fever seroprevalence in ruminant was wide and there was a heterogeneity among the articles which were enrolled in this meta-analysis (I^2 = 88.9%), so a random effect model was used.

Pooling of the data from nine eligible studies yielded the overall point estimate of Q fever prevalence of 27% (95% confidence interval [CI]: 23%–32%) (χ^2 = 162.78, df = 18, P < 0.0001).

Figure 2 in a forest plot framework shows that the pooled estimation of Q fever prevalence among goats (33%, 95% CI: 22%–45%) were higher than the cattle (17%, 95% CI: 5%–28%) and sheep (27%, 95% CI: 21%–32%).

As shown in Figure 3, the overall pooled Q fever prevalence among female goats and sheep were 28% (95% CI: 24%–32%) and 27% (95% CI: 20%–34%), respectively. While pooled estimates of this infection among male goats were 26% (95% CI: 5%–47%) and among male sheep was 23% (95% CI: 15%–31%).

Molecular studies

Overall, 14 molecular studies were identified, of which four were not included in the meta-analysis; in a study, there was no positive blood sample from ruminants, dog, hedgehog, and humans tested by PCR.[36] Another survey reported that 10.76% of camel blood samples were PCR positive for *C. burnetii*.[33] In the third article, *C. burnetii* DNA was detected in 12.53% and 16.39% of ovine and caprine aborted fetuses by nested PCR, respectively.[34] The prevalence was higher by real time PCR. In another research in Kerman, southeast of Iran, 160 ticks were collected from ruminants, from which 3 pools of five female of *Hyalomma anatolicum anatolicum* and one pool of three *Rhipicephalus sanguineus* were found to be positive.[32] These articles were not included in the meta-analysis due to lack of adequate data for pooling. Hence, ten studies were included in our meta-analysis which all of them looked for C. *burnetii* in milk samples from ruminants.[22-31]

Overall, 1852 bulk tank milk (957 cattle, 433 sheep, and 462 goats) and 87 individual samples (64 goats and 23 sheep) were included in the Meta analysis. 9.72%, 2.54%, and 2.6% bulk milk samples from cattle, sheep, and goat were positive, respectively. 40% and 34.8% of individual milk samples of goats and sheep were positive, respectively. The quality scores of the articles were from 12 to 19. In most studies, the pathogen was detected in milk samples using an assay designed to detect gene com1. 16S rRNA and element IS1111 were used in one and two surveys respectively.[27,28] Table 2 summarizes the characteristics of the studies.

We used a random effect model because there was a heterogeneity among the papers which were included in this analysis (I^2 = 87.04, Chi-square = 185.21, df = 24 and P < 0.001). After pooling the data, the prevalence

Table 1: Characteristics of the serological studies included in the study

Author	Year	City	Population	Sample size	Percentage positive	Number of flock	Quality score
Khalili and Sakhaee[10]	2009	Kerman	Dairy cow	93	10.75	12	12
			Goat	76	65.78	9	
Azizzadeh *et al.*[11]	2014	Khorassan Razavi	Dairy cow	246	22.30	19	22
Esmaeili *et al.*[12]	2014	Ardebil	Sheep	253	33.60	32	18.5
Sakhaee and Khalili[13]	2010	Kerman	Sheep male	42	21.43	10	12.5
			Sheep female	43	37.21	10	
Esmaeili *et al.*[14]	2013	Mazandaran	Sheep male	24	16.70	-	18
			Sheep female	229	24.50	-	
Ezatkhah *et al.*[15]	2015	Southeast Iran	Sheep male	28	17.90	50	22
			Sheep female	99	38.40	50	
			Goat male	112	16.10	50	
			Goat female	129	27.90	50	
Rad *et al.*[16]	2014	Khorassan	Sheep male	48	36.2	29	24
			Sheep female	207	36.6	29	
			Goat male	40	37.5	28	
			Goat female	165	28.2	28	
Pourmahdi *et al.*[17]	2013	Ahwaz	Sheep female	220	13.18	9	23
Asadi *et al.*[18]	2013	Iran	Sheep with a history of abortion	1100	19/5	-	21
			Goat with a history of abortion	180	27/2	-	
Aflatoonian*[21]	2014	Kerman	High risk population	64	7.8	-	22
Khalili *et al.**[20]	2014	Kerman	High risk population	75	68	-	17
Esmaeili *et al.**[19]	2014	Kurdistan	High risk population	250	27.83		18
Khalili *et al.**[35]	2011	Kerman	Bulk milk cow	44	45.4	44	13

*The papers were not included in the meta-analysis

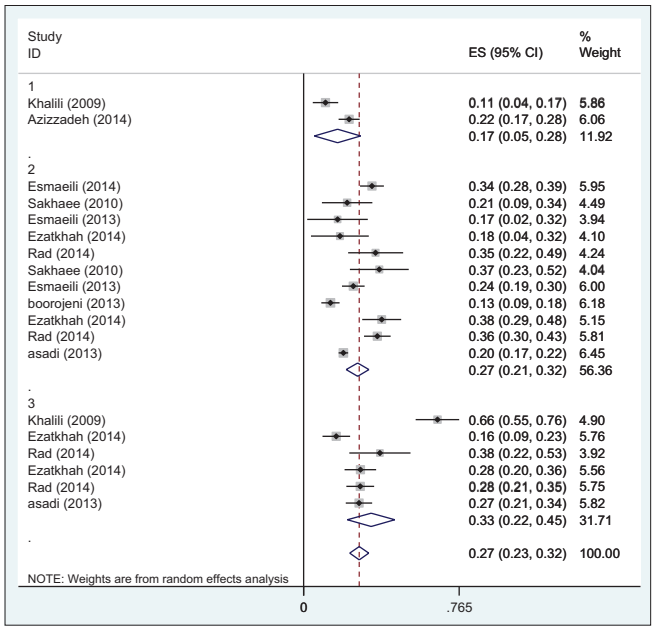

Figure 2: The result of meta-analysis of seroprevalence studies on *Coxiella burneti* in Iran from the year 2000 to 2015. Pooled Q fever seroprevalence among goats (Group 3) were higher than cattle (Group 1) and sheep (Group 2) (ES = Estimated seroprevalence of *Coxiella burneti*)

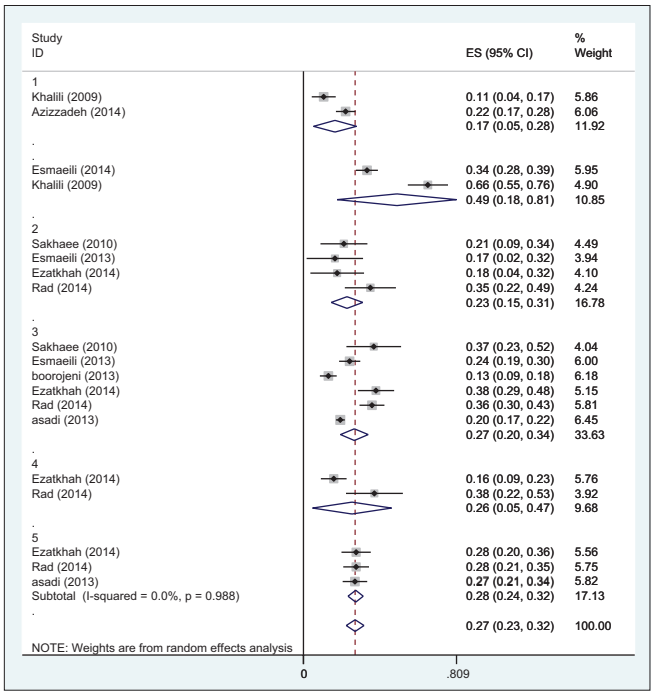

Figure 3: The result of meta-analysis of seroprevalence studies on *Coxiella burnetii* in Iran from the year 2000 to 2015. Pooled Q fever seroprevalence among female goats (Group 5) and sheep (Group 3) was higher than male goats (Group 4) and sheep (Group 2). The dairy cattle (Group 1) and small ruminants (without mention to sex) (.) showed minimum and maximum seroprevalence the infection, respectively. (ES = Estimated seroprevalence of *Coxiella burnetii*)

of *C. burnetii* DNA in milk samples (regardless of bulk or individual samples) of ruminants was 5% (95% CI: 3%– 9%). Sensitivity analysis was performed, after

Table 2: Characteristics of molecular studies included in the study

Author	Year	City	Sample	Gene	Sample size	Percentage positive	Number of flock	Quality score
Rahimi *et al.*[22]	2010	Chaharmahalva Bakhtiari	Bulk milk cow	Com 1	210	6.2	28	17
			Bulk milk sheep	Com 1	110	0	31	
			Bulk milk goat	Com 1	56	1.8	20	
Ghalyanchi *et al.*[23]	2013	Qom	Bulk milk cow	Com 1	100	14	-	13
Kargar *et al.*[24]	2013	Jahrom	Bulk milk cow	Com 1	100	11	-	19
Rahimi *et al.*[25]	2011	Isfahan	Bulk milk cow	Com 1	247	3.2	90	17
			Bulk milk sheep	Com 1	140	5.7	42	
			Bulk milk goat	Com 1	110	4.5	32	
Khademi *et al.*[26]	2014	Bonab	Bulk milk cow	Com 1	100	26	100	12
Kargar *et al.*[27]	2013	Jahrom	Bulk milk cow	Is1111	70	17.14	-	12
			Bulk milk cow	16S	70	10	-	
Khanzadi[28]	2014	Mashhad	Bulk milk cow	Is1111	60	3.33	-	13
			Goat milk	Is1111	10	0	-	
			Sheep milk	Is1111	23	34.78	-	
Rahimi[29]	2014	Fars	Bulk milk sheep	Com 1	30	0	8	15
		Qom	Bulk milk sheep	Com 1	20	0	9	
		Kerman	Bulk milk sheep	Com 1	34	0	8	
		Khuzestan	Bulk milk sheep	Com 1	41	0	13	
		Yazd	Bulk milk sheep	Com 1	58	5.2	21	
Rahimi[30]	2010	Fars	Bulk milk goat	Com 1	60	6.7	22	14
		Qom	Bulk milk goat	Com 1	36	0	10	
		Kerman	Bulk milk goat	Com 1	50	0	15	
		Khuzestan	Bulk milk goat	Com 1	90	1.1	24	
		Yazd	Bulk milk goat	Com 1	60	1.7	18	
Khademi *et al.*[31]	2014	Khorramabad	Goat milk samples (not bluk)	Com 1	54	48.15	8	15
Bashiribod *et al.**[36]	2008	Mazandaran	Ticks/dogs/hedgehog/rminants/hman	Non clear	1052	0	-	10
Doosti *et al.**[33]	2014	Isfahan	Camale	16 SrRNA	130	10.76	-	11
Fard *,¶[32]	2011	Kerman	Ticks	Is1111	160	-	-	13
Dehkordi*,#[34]	2011	Iran	Caprine aborted fetuses	Com 1	744	16.39	48	16
			Caprine aborted fetuses	Is1111	744	20.43	48	
			Ovine aborted fetuses	Com 1	782	12.53	60	
			Ovine aborted fetuses	Is1111	782	15.47	60	

*Not included in the meta-analysis; ¶3 pools of five female of *Hyalomma anatolicum anatolicum* and one pool of three *Rhipicephalus sanguineus* were found to be positive; #In this study, the prevalence of *Coxiella burnetii* in aborted ovine, and caprine fetuses were detected by the nested and real-time PCR. The com 1 and IS1111 were used for the nested PCR and real time PCR respectively. PCR = Polymerase chain reaction

removing two studies which used individual milk samples.[28,31] the prevalence rate was 4% (95% CI: 2%– 6%). Figure 4 shows that the prevalence among cattle (10%, 95% CI: 6%– 16%) was higher than sheep (2%, 95% CI: 0–7%) and goats (4%, 95% CI: 0–12%).

As shown in Figure 5, for detection of *C. burnetii* DNA, the assays designed based on IS1111 element (11%, 95% CI: 1%–27%) showed the higher prevalence in comparison with the assays designed based on single copy genes such as com1 gene (4%, 95% CI: 2%–8%). Sensitivity analysis was performed, after removing the two studies on individual milk samples.[28,31] The prevalence rate for IS1111 was higher than com1.

DISCUSSION

In this survey, we assessed all serological and molecular studies on *C. burnetii* in Iran to identify the epidemiologic features of the infection in our country. Serological tests only detect antibodies against *C. burnetii*, as a matter of fact, they show the previous exposure to the bacteria but not necessarily the shedding of the pathogen. Molecular assays can detect the microorganism and confirm the shedding of the bacteria, and thus a current infection.

Serological studies

The serological data assessed in this study demonstrated that the overall seroprevalence of *C. burnetti* infections in different parts of Iran is variable from one area to another. This heterogeneity in the prevalence could be due to differences in sample sizes, design of the studies, and the sensitivities of the tests. Moreover, it may reflect agricultural or climatic differences between different areas in our country. In animals as well as in humans, most *C. burnetii* infections are asymptomatic therefore the overall prevalence of infection is often unknown. Similar wide variation in Q

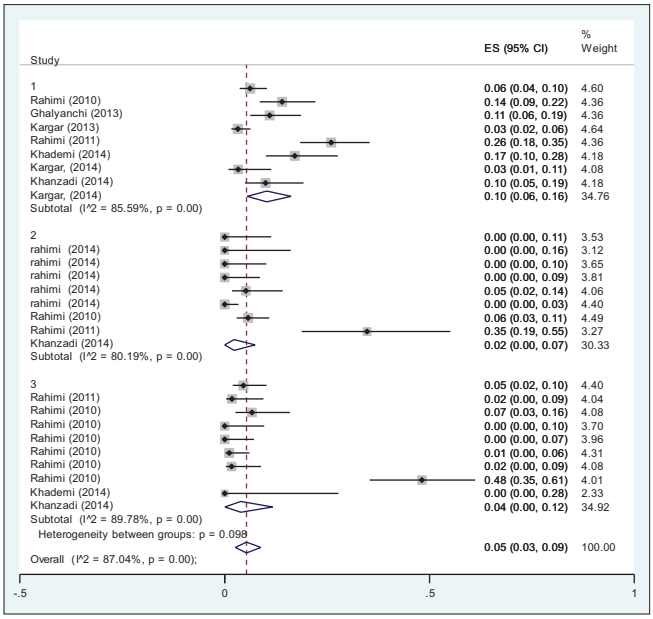

Figure 4: The result of meta-analysis of prevalence studies on *Coxiella burnetii* DNA in Iran from the year 2000 to 2015. The prevalence of *Coxiella burnetii* DNA in milk samples of cattle (Group 1) was higher than sheep (Group 2) and goats (Group 3) (ES = Estimated prevalence of *Coxiella burnetii*)

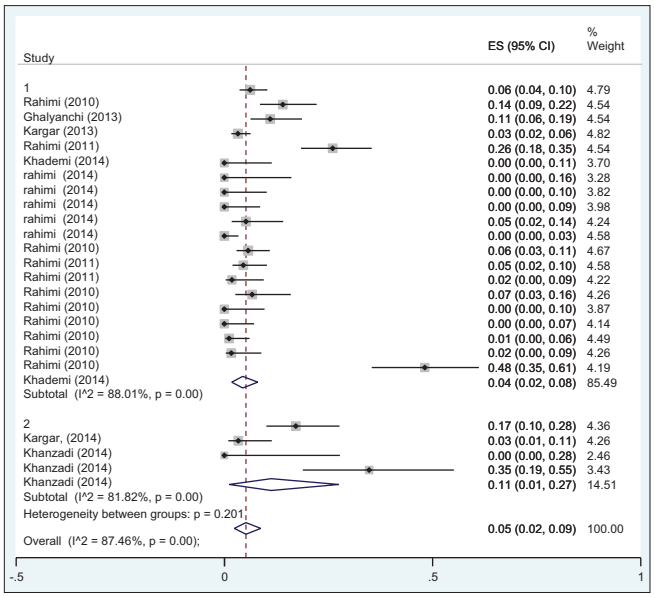

Figure 5: The result of meta-analysis of prevalence studies on *Coxiella burnetii* DNA in Iran from the year 2000 to 2015. For the detection of *Coxiella burnetii* DNA, the assays designed based on IS1111 element (Group 2), showed the higher capability in combination with com 1 PCR assay (Group 1) (ES = estimated prevalence of *Coxiella burnetii*)

fever seroprevalence was reported from other countries, even in areas of proximity. Regional differences in the prevalence of the infection were observed in Bulgaria.[37] and Germany.[38] A study in Sweden and a systematic review in Africa revealed that seroprevalence of *C. burnetii* infection is different, depending on the geographic location.[39,40] However, in a study in Turkey, no association was observed between geographical variations and seroprevalence of the infection.[41]

The serological data reviewed in our study revealed a relatively high seroprevalence of *C burnetii* infection among ruminant. It is a considerable issue because the people who have close contact with infected livestock are at increased risk of infection. In the present study, the seroprevalence of infection in small ruminants was higher than cattle. Goats, sheep, and cattle are the main source of human infection and many studies have assessed *C. burnetii* infection in these three groups. These studies have shown that the infection in ruminants varies with species tested. In a study in Reunion Island, the overall seropositivity was reported 11.8%, 1.4%, and 13.4% in cattle, sheep, and goats, respectively.[42] The seroprevalence of *C. burnetii* in ruminants in Mexico was reported to be 28% for the dairy cattle, 10% for beef cattle, 35% for goats, and 40% for sheep.[43] In a study, the seroprevalence of *C. burnetii* among livestock in Afghanistan was 43.4% for sheep, 52.7% for goats, and 5.2% for cattle.[44] In Togo, 14.8% of cattle, 14.4% of sheep, and 8.3% of goats were positive for *C. burnetii*.[45] The lower prevalence observed in cattle in this study may be due to differences in the condition of livestock keeping. In Iran, the small ruminants are moving during spring and summer in grasslands, which increase the risk of their contact and transmission of the pathogen between neighboring herds. However, cattle is always kept in their farm, which reduces the contact between herds. Moreover, cattle farms usually have calve place, and animals are surveyed there during pregnancy and delivery when shedding of bacteria by infected animals is high.

Results showed that pooled Q fewer seroprevalence among females was higher than males. Similar results in seroprevalence of antibody against *C. burnetii* were reported from some studies. In Turkey, it was shown that the seroprevalence of Q fever was lower in males than in females in both cattle and sheep.[41] In Cameroon, seroprevalence of *C. burnetii* was higher in female cows.[46] This microorganism has a high affinity for the uterus and mammary glands, and large numbers of pathogen are found in these tissues, so this is not surprising that the seroprevalence of *C. burnetii* infection is greater in females. However, there is evidence that 17 β-estradiol in female animals have protective effects.[47] More studies are needed to make a better understanding of the role of sex in this infection.

Molecular studies

Our results showed that the bacteria present in milk in 5% of the herds. Drinking contaminated raw milk does not seem to be an important route of disease transmission; moreover, pasteurization of milk and

dairy products is routinely carried out in Iran. However, raw unpasteurized milk and other dairy products are commonly available in some regions, especially rural areas and it could be a potential risk for disease transmission. The present study shows a higher prevalence of C. *burnetii* DNA in milk samples from cattle than milk from small remnants. This result is similar to that obtained in Portugal.[48] In other countries, rate of shedding of *C. burnetii* through milk were ranging from 18.8% to 94.3% and 0% to 32.9% for cattle and small ruminants, respectively.[48-55] These studies revealed that *C. burnetii* shedding in milk is widespread in herds in different regions of the world.

Our results showed the higher occurrence of PCR positivity in cattle but greater seropositivity in small ruminants. The high shedding prevalence among cattle could be explained by the long-time excretion of bacteria through milk, which, in cows, can be extended for a long time (over many months or even years) compared with the shorter excretion periods in small ruminants (several months).[49,56] Moreover, it seems that the shedding of bacteria in milk is less important in small ruminants.[56] In sheep and goats *C. burnetii* is strongly shed after abortion or parturition in birth products.[54]

Our results indicated higher prevalence of *C. burnetii* DNA in the PCR assay with gene IS1111 in comparison with other assays designed based on single copy genes. Other studies have shown similar results.[49,57,58] Several genes such as plasmid sequences, chromosomal genes such as isocitrate-dehydrogenase, the outer membrane protein coding gene com1, the superoxide dismutase gene, and the transposase gene in insertion element IS1111 are used to detect *C. burnetii* in PCR-based assays. IS1111 element is a preferred marker for PCR assays, as it is present in multiple copies within the genome, therefore the use of this gene enhances sensitivity of detection.[59]

Various factors such as the potential drawback of the random-effects model that was used in this study, limitations of the individual studies included in meta-analysis (e.g., small sample size and the method of reporting the results), unpublished studies, lack of interest by authors to submit the negative results for journals, strongly tendency of reviewers and editors to reject negative studies might be influenced our results. However, it seems this paper could be to provide an accurate and impartial description of the Q fever infection in Iran.

CONCLUSIONS

This review showed that *C. burnetii* DNA or its antibodies were frequently reported among ruminants during recent years in Iran. This pathogen is a potential threat for both livestock industry and human health, thus policy makers should have a plan to monitor and control the infection, especially in livestock.

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Conflicts of interest
There are no conflicts of interest.

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