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REGULAR ARTICLES

Molecular prevalence of *Coxiella burnetii* in milk in Iran: a systematic review and meta-analysis

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Abstract

Q fever is a major zoonotic disease in the world. The aim of this meta-analysis was to estimate the prevalence of *Coxiella burnetii* in animal milk in Iran. We systematically reviewed the literature to identify eligible studies from January 2008 to June 2016 in English or Farsi (Persian) databases. We extracted the molecular prevalence of *C. burnetii* in milk from cows, goats, sheep, and camels in Iran. The total prevalence of *C. burnetii* in cow milk was 15.09% (95% CI 11.08–19.10) by PCR methods. The highest and lowest prevalence of Q fever agent were seen in the East Azerbaijan (25.55%) and Khorasan-Razavi (4.22%) provinces, respectively. The molecular prevalence of *C. burnetii* in goat milk was 7.80% (95% CI 3.54–12.07%). The provinces of Qom (0%) and Lorestan (44.71%) had the lowest and the highest frequency of *C. burnetii* infection in goat's milk, respectively. Total prevalence of *C. burnetii* in sheep milk was 3.79% (95% CI 0.72–6.87%). The highest frequency of *C. burnetii* in sheep milk was detected in the Khorasan-Razavi province (34.78%). The frequency of *C. burnetii* in camel milk was 1.43%. High infection of *C. burnetii* in milk is an important health problem in Iran, amplified by the traditional preparations of dairy products.

Keywords *Coxiella burnetii* · Q fever · Animal · Iran · Milk · Dairy

Introduction

Coxiella burnetii is the causative agent of Q fever, a major worldwide zoonotic disease. Q fever is a public health problem in many countries and especially in people in contact with livestock animals including cattle, sheep, and goats (Angelakis and Raoult 2010). Q fever infection in animals is mostly asymptomatic but can cause abortion or stillbirth in severe cases. In infected animals, *C. burnetii* sheds into the environment through the milk, feces, urine, and especially in birth products (Guatteo et al. 2011; Rodolakis 2009).

Inhalation of contaminated aerosols or dusts containing *C. burnetii* is the main route of transmission to human (Eldin et al. 2017). People in contact with newborn animals, placenta, or parturient fluid from infected animals are particularly at risk for acquiring Q fever. However, humans may also be contaminated through consumption of *C. burnetii*–contaminated milk and dairy products (Angelakis and Raoult 2010; Parker et al. 2006). In human, Q fever is often manifested in two forms, acute and chronic (Anderson et al. 2013). Acute Q fever is a flu-like and self-limited illness. The fatality rate of acute Q fever is reported to be 1–2% in severe forms (myocarditis, sever hepatitis, sever pneumonia, and encephalitis) (Parker et al. 2006). Chronic Q fever is accompanied with symptoms such as endocarditis, vasculitis, osteomyelitis, abortion, and stillbirth. In the absence of appropriate treatment for patients with endocarditis and vasculitis, the death of the patients will be inevitable (Anderson et al. 2013; Raoult 2012).

Coxiella burnetii is shed in milk by infected livestock (cattle, sheep, goats, and camels) for variable periods (Guatteo et al. 2006). Milk can also become contaminated by fecal materials or by contact with the site of infection in the

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periparturient and/or lactating animal. Ingestion of contaminated milk or dairy products can also be an alternative source of infection (Petruzzelli et al. 2013). Consumption of contaminated product may further lead to seroconversion and, in a few cases, to Q fever disease (Rodolakis 2009).

Based on different studies, Q fever is an endemic disease in the Iran (Mobarez et al. 2017). Acute and chronic cases of Q fever have recently been reported in different parts of the country (Esmaeili et al. 2017; Ghasemian et al. 2016; Khalili et al. 2016; Yaghmaie et al. 2015). Furthermore, in recent years, various instances of milk contaminated by *C. burnetii* have been reported in Iran. However, an overall estimate for the prevalence of the disease in Iran does not exist. The aim of this study was to estimate the prevalence of *C. burnetii* in the milk samples in Iran. An overall estimation of *C. burnetii* in milk samples will help health policy makers modify control and prevention programs for Q fever in Iran.

Methods

Information sources and search

We searched the literature for articles that reported the prevalence of *C. burnetii* in milk from domestic animals (cow, goat, sheep, and camel) in Iran from January 2008 to June 2016.

Multiple English and Farsi (Persian) electronic data sources were searched including Google Scholar, Medline/PubMed, Science Direct, Scopus, Web of science, Iranmedex, Scientific Information Database (SID), Magiran, and Iranian Research Institute for Information Science and Technology (IRANDOC). In addition, the citations of the included articles from these databases were reviewed to find other relevant studies. We also looked at the electronic abstract list of congress conducted in Iran and also at the electronic database of students' thesis and unpublished researches with email to researchers. The keywords that we used for our search were "Q fever, *Coxiella burnetii*, milk, dairy, and Iran."

Eligibility criteria and study selection

Articles with cross-sectional design that chose sample groups from Iran, published in Farsi (Persian) or English, and detected Q fever with molecular assays (PCR) were eligible to enter meta-analysis.

Exclusion criteria for studies from this systematic review were as follows: (1) lack of access to full article and insufficient data in abstract, (2) lack of *C. burnetii* molecular test detection (serological testing only), (3) sampling products other than milk, and (4) review articles.

We contacted the corresponding author when we had questions about the published data or concerns about the eligibility of the article.

Validity assessment

Five criteria were used for the assessment of the quality of reporting, chosen from Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement: A. the eligibility criteria for included animals (doing study in Iran); B. a clear definition of outcome, i.e., prevalence of *Coxiella* detected in milk; C. description of locations, settings, and relevant dates of studies; D. a report of the number of interested outcomes; and E. the validity of the data collection (Sargeant et al. 2016; Vandenbroucke et al. 2007).

Data collection and data items

Data was extracted by two researchers and categorized based on the following criteria: type of study, sample size, location and time of the study, species, and prevalence of *C. burnetii* in milk samples. The studies were also grouped based on host animal, namely sheep, goat, cow, and camel.

Analytic approach

We conducted meta-analyses in STATA version 12. Meta-analysis was performed for prevalence of *C. burnetii* in milk from livestock animals in Iran. The outcome was measured and reported as prevalence, with point and 95% confidence intervals. A Q test was used to assess heterogeneity. When the heterogeneity test had a p value less than 0.1, a random-effects model was used; otherwise, the fixed-effects model was used to calculate the global prevalence. Also, by calculating global prevalence of *C. burnetii* in each province, we mapped prevalence of *C. burnetii* in milk using ArcGIS ver. 10.2.

Results

Search results

As presented in Fig. 1, we found 168 abstracts in our literature review (Fig. 1). After removing duplications ($n = 87$) based on title and abstract, 81 remained for full-text review. Of those, 57 articles were excluded based on the selection criteria, mainly relying on serological test ($n = 32$), being review article ($n = 8$), or other kind of study ($n = 2$), study on *C. burnetii* in countries other than Iran ($n = 3$), and no access to full-text article ($n = 1$). The shortlist contained 24 articles for meta-analysis (Table 1).

Prevalence of *C. burnetii* in cow milk

The global prevalence of *C. burnetii* in cow milk was 15.09% (95% CI 11.08–19.10) by PCR methods (Table 2,

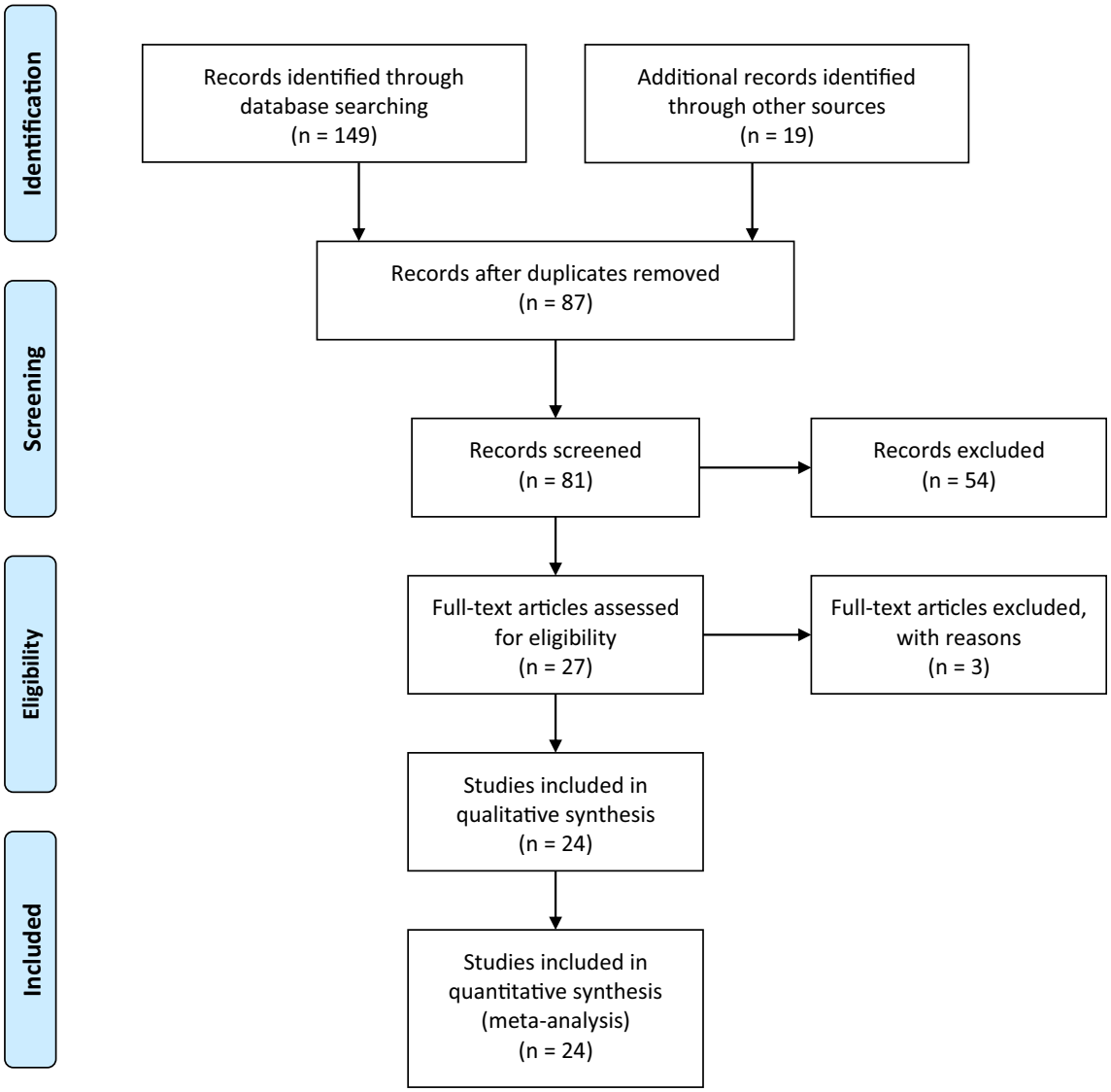

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Fig. 1 PRISMA flow diagram (included and excluded records)

Fig. 2). The prevalence of *C. burnetii* in cow milk was reported from 11 provinces of Iran (Fig. 3). Significant publication bias ($p < 0.001$) and high heterogeneity (I2 = 89.75, Q test $p < 0.0001$) were observed. Meta-regression analysis showed that this high heterogeneity showed no significant association with the geographical locations of the studies ($\beta = 0.006$, $p = 0.85$). The highest and lowest prevalence of Q fever agent were seen in the East Azerbaijan (25.55%) and Khorasan-Razavi (4.22%) provinces, respectively.

Prevalence of *C. burnetii* in goat milk

The global prevalence of *C. burnetii* in goat milk was 7.80% (95% CI 3.54–12.07%) in Iran by PCR methods (Fig. 4). Significant publication bias ($p = 0.011$) and high

Table 1 Characteristics of the included studies in the systematic review, 2008–2016

	Authors	Location (province)	Species	Sample size	Number of positive samples	Conducted study years (references)
1	Ahmadizadeh et al.	Tehran	Cow	150	18	2014 (Ahmadizadeh et al. 2015)
2	Ghalyanchi Langeroudi et al.	Qom	Cow	100	14	2011 (Ghalyanchi Langeroudi et al. 2013)
3	Borji et al.	Khorasan-Razavi	Cow	100	5	2013 (Borji et al. 2014)
4	Rahimi et al.	Chaharmahal-va-Bakhtiari	Cow Goat Sheep	210 56 110	13 1 0	2008 (Rahimi et al. 2010)
5	Haghi et al.	Zanjan	Cow Sheep	38 22	5 2	2014 (Haghi et al. 2015)
6	Khademi et al.	East Azerbaijan	Cow	100	26	2014 (Khademi et al. 2014a)
7	Khademi et al.	East Azerbaijan	Cow	80	20	2014 (Khademi et al. 2015)
8	Khanzadi et al.	Khorasan-Razavi	Cow Sheep	60 23	2 8	2012 (Khanzadi et al. 2014)
9	Nasehfar et al.	Yazd	Cow	100	5	2013 (Nasehfar et al. 2015a)
10	Kargar et al.	Fars	Cow	100	11	2009 (Kargar et al. 2013)
11	Rahmde et al.	Fars	Cow	100	6	2013 (Rahmde et al. 2014)
12	Rahimi et al.	Isfahan	Cow Goat Sheep Camel	247 110 120 70	8 8 5 1	2010 (Rahimi et al. 2011)
13	Nasehfar et al.	Yazd Isfahan Chaharmahal-va-Bakhtiari	Cow Cow Cow	100 100 100	15 26 33	2014–2015 (Nasehfar et al. 2015b)
14	Kargar et al.	Fars	Cow	70	12	2010 (Kargar et al. 2015)
15	Alipour et al.	Khuzestan	Cow	86	4	2011 (Alipour 2011)
16	Khademi et al.	Lorestan	Cow	83	41	2014 (Khademi 2014)
17	Etemadfar et al.	Lorestan	Cow	120	9	2015 (Etemadfar 2016)
18	Karimian et al.	ShahreKord	Cow	50	16	2014 (Karimian et al. 2016)
19	Abbasi et al.	Fars Chaharmahal-va-Bakhtiari Yazd Qom Kerman	Goat Goat Goat Goat Goat	60 90 60 36 50	4 1 1 0 0	2010 (Abbasi et al. 2011)
20	Khademi et al.	Lorestan	Goat	54	20	2013 (Khademi et al. 2014b)
21	Jaydari et al.	Lorestan	Goat	51	21	2013–2014 (Jaydari et al. 2014)
22	Khalili et al.	Kerman	Goat	31	5	2011 (Khalili et al. 2015)
23	Rahimi	Fars Qom Kerman Khuzestan Yazd	Sheep	30 20 34 41 58	0 0 0 0 3	2010 (Rahimi 2014)
24	Lorestanani et al.	Lorestan	Sheep	72	15	2013–2014 (Lorestani et al. 2016)

heterogeneity (I2 = 90.05, Q test $p < 0.001$) were observed in this case. Meta-regression analysis showed that this high heterogeneity had no significant association with the geographical locations of the studies ($\beta = 0.051$, $p = 0.49$). Investigation of *C. burnetii* was conducted in 8 provinces. The provinces of Qom (0%) and Lorestan (44.71%) had the lowest and the highest frequency of *C. burnetii* in goat milk, respectively, as detected by PCR (Fig. 5).

Table 2 Prevalence of *C. burnetii* in milk domestic animals of by molecular methods in Iran, 2008–2016

	Number of included studies	Total number of tested milk samples	Global estimate (%) (95% CI)
Cow	16	2004	15.09 (11.08–19.10)
Goat	6	598	7.80 (3.54–12.07)
Sheep	6	550	3.79 (0.72–6.87)
Camel	1	70	1.43 (0.07–6.84)

Prevalence of *C. burnetii* in sheep milk

The global prevalence of *C. burnetii* in sheep milk was 3.79% (95% CI 0.72–6.87%), as detected by PCR methods (Fig. 6). There was no significant publication bias ($p = 0.323$) and high heterogeneity (I2 = 78.40, Q test $p = 0.002$) were observed. Meta-regression analysis showed that this high heterogeneity was not significantly associated with the geographical locations of the studies ($\beta = -0.73$, $p = 0.07$). The investigation of *C. burnetii* in sheep milk was conducted in 10 provinces and this bacterium was detected in 5 provinces by PCR tests. The causative agent of Q fever was not found in samples from the provinces of Chaharmahal-va-Bakhtiari, Fars, Qom, Kerman, and Khuzestan. The highest frequency of *C. burnetii* in sheep milk was detected in Khorasan-Razavi province (34.78%) (Fig. 7).

Prevalence of *C. burnetii* in camel milk

Only one study was conducted in Iran about *C. burnetii* in camel milk in which 1.4% (95% CI 0.07–6.84) of camel milk samples had positive for *C. burnetii* in Isfahan province.

Discussion

This is the first systematic review and meta-analysis of the prevalence of *C. burnetii* in milk in Iran. We estimated that the overall prevalence of *C. burnetii* is 15.1%, 7.8%, 3.8%, and 1.4%, in milk samples from cows, goats, sheep, and camel, respectively. The prevalence is compatible with previously reported high Q fever prevalence in domestic animals: 13.3%,

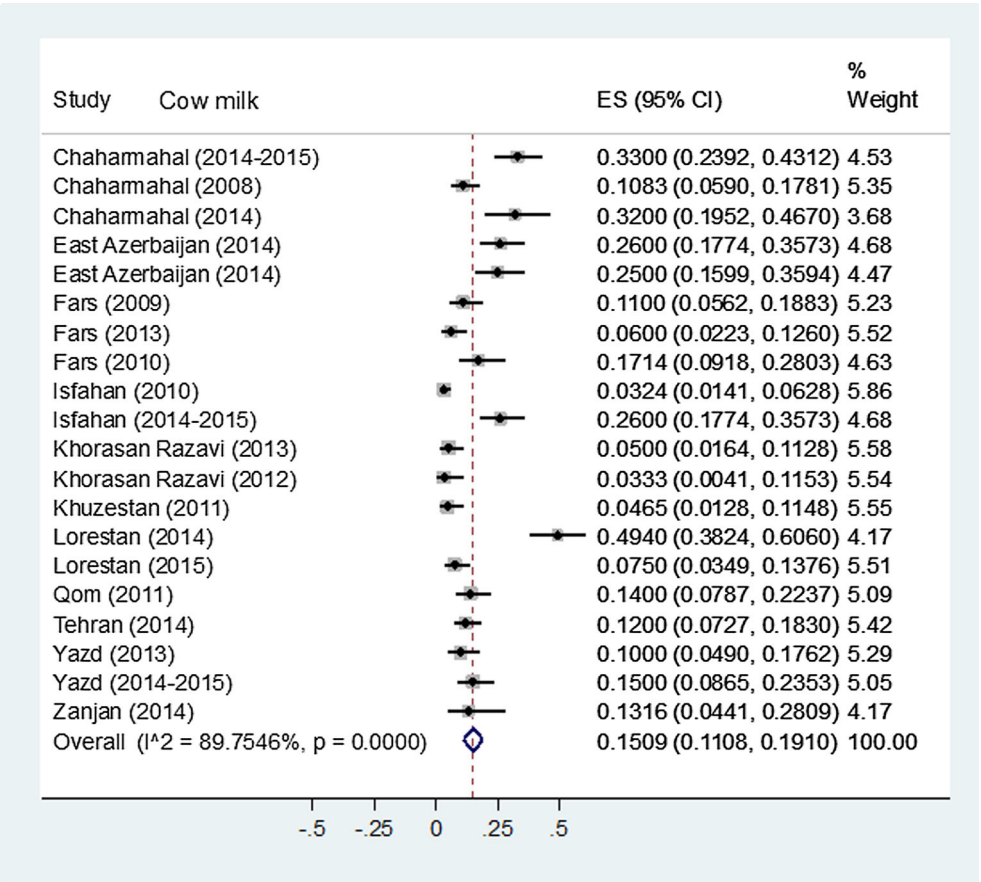

Fig. 2 Forest plot for the prevalence of *C. burnetti* in cow milk in Iran

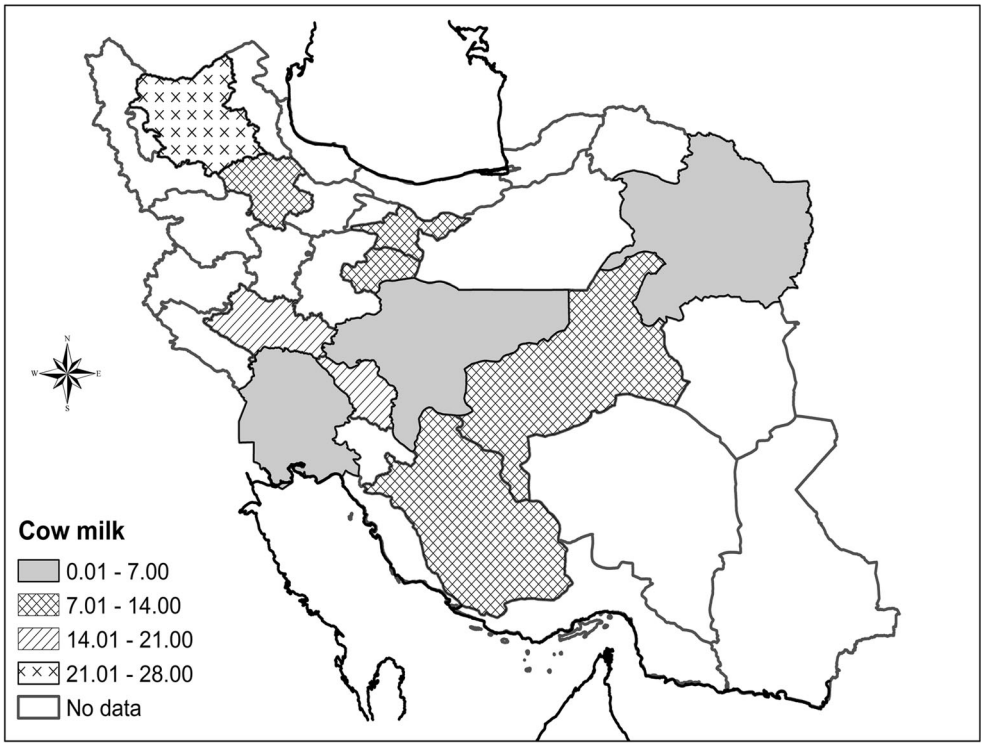

Fig. 3 Geographical distribution of C. *burnetti* in cow milk by Arc GIS

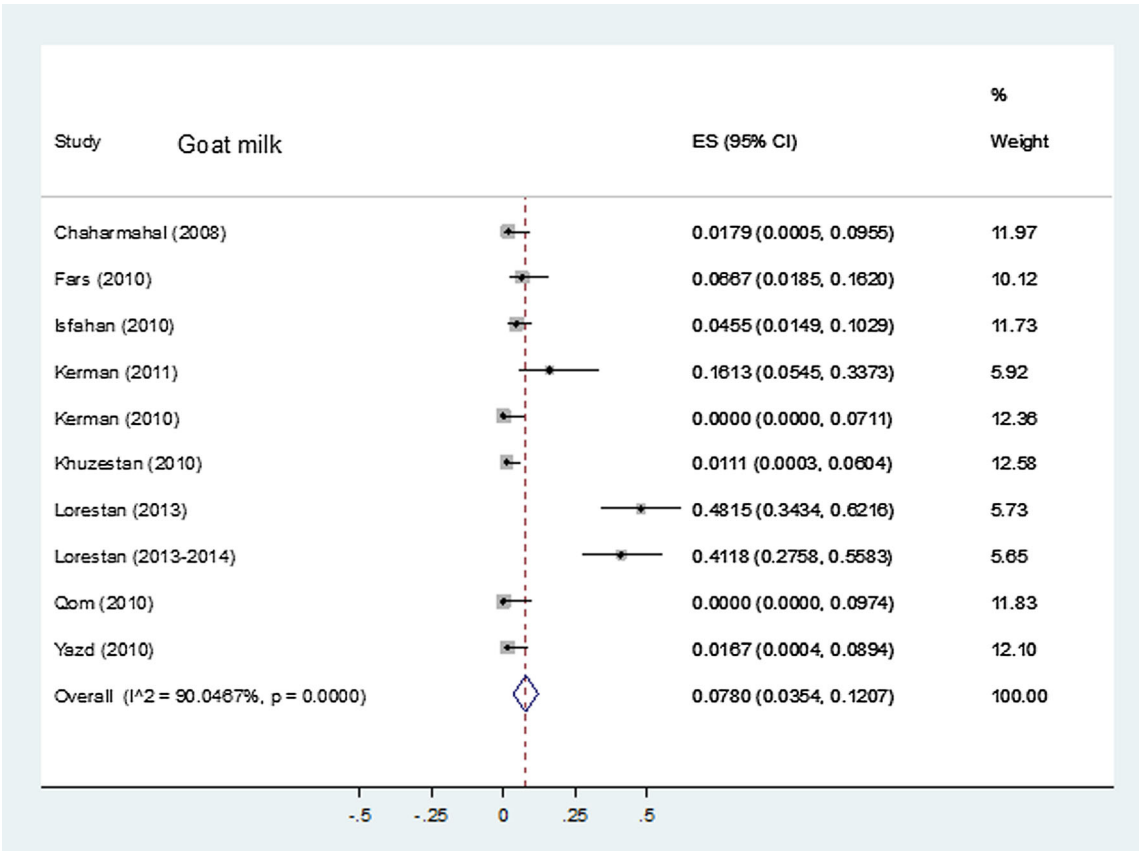

Fig. 4 Forest plot for the prevalence of *C. burnetti* in goat milk in Iran

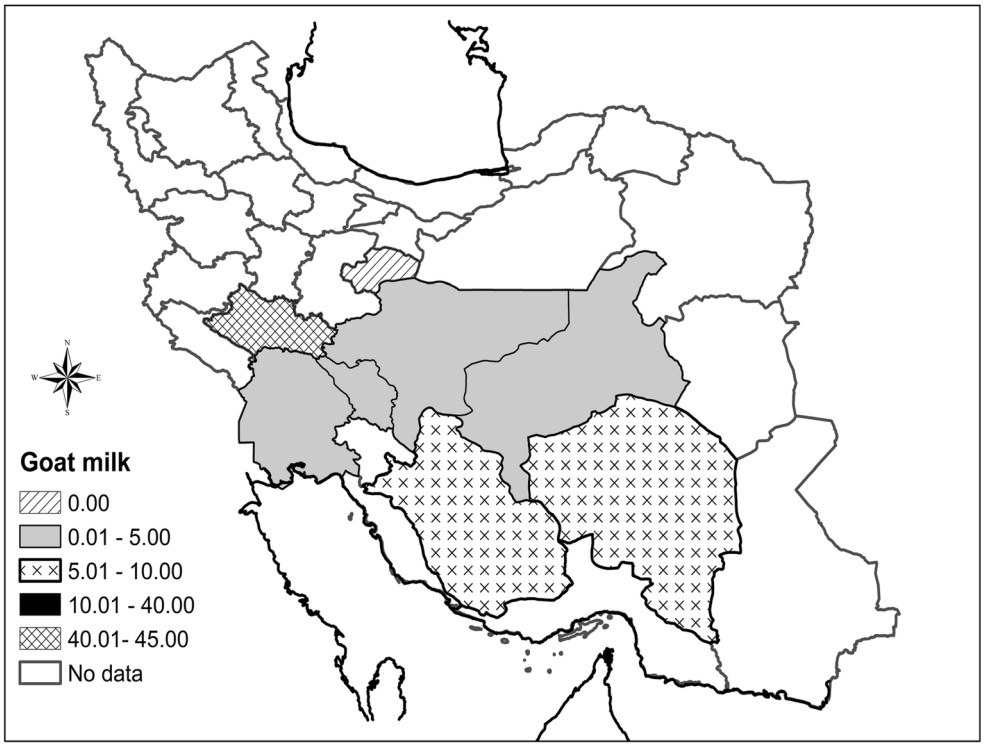

Fig. 5 Geographical distribution of *C. burnetti* in goat milk by Arc GIS

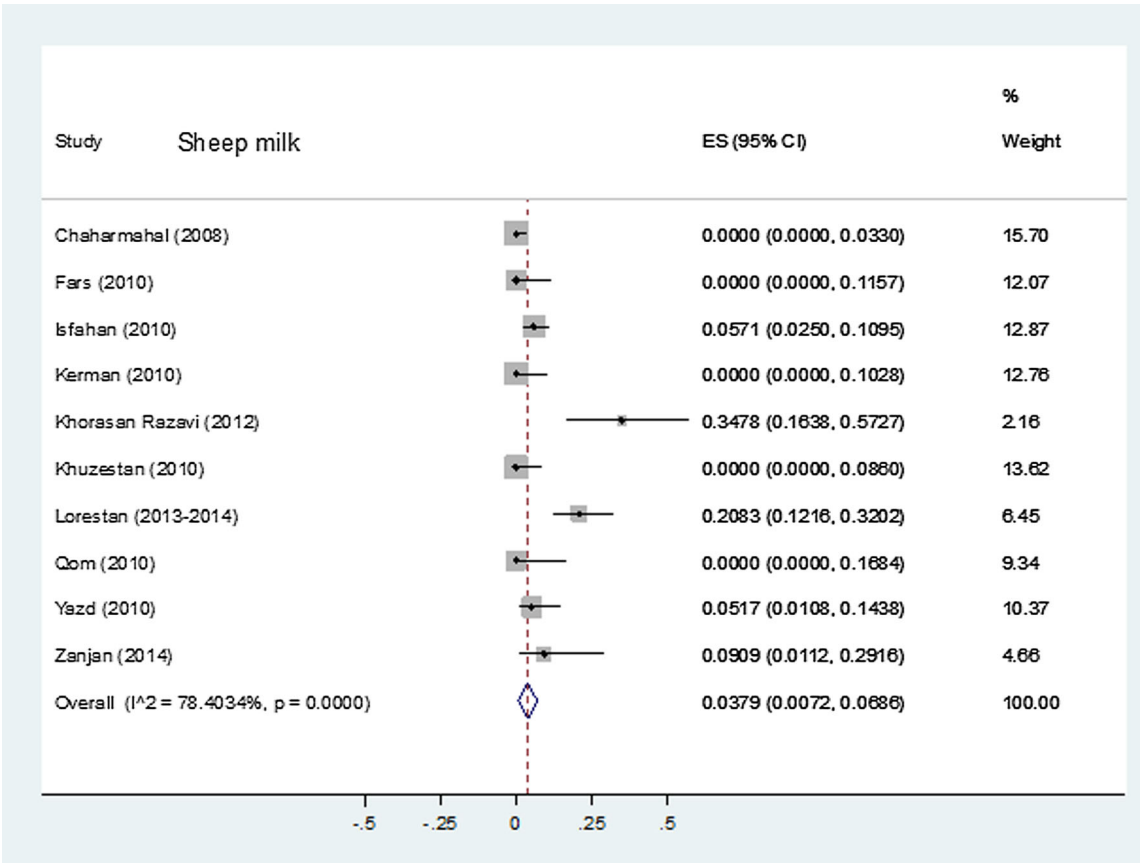

Fig. 6 Forest plot for the prevalence of *C. burnetti* in sheep milk in Iran

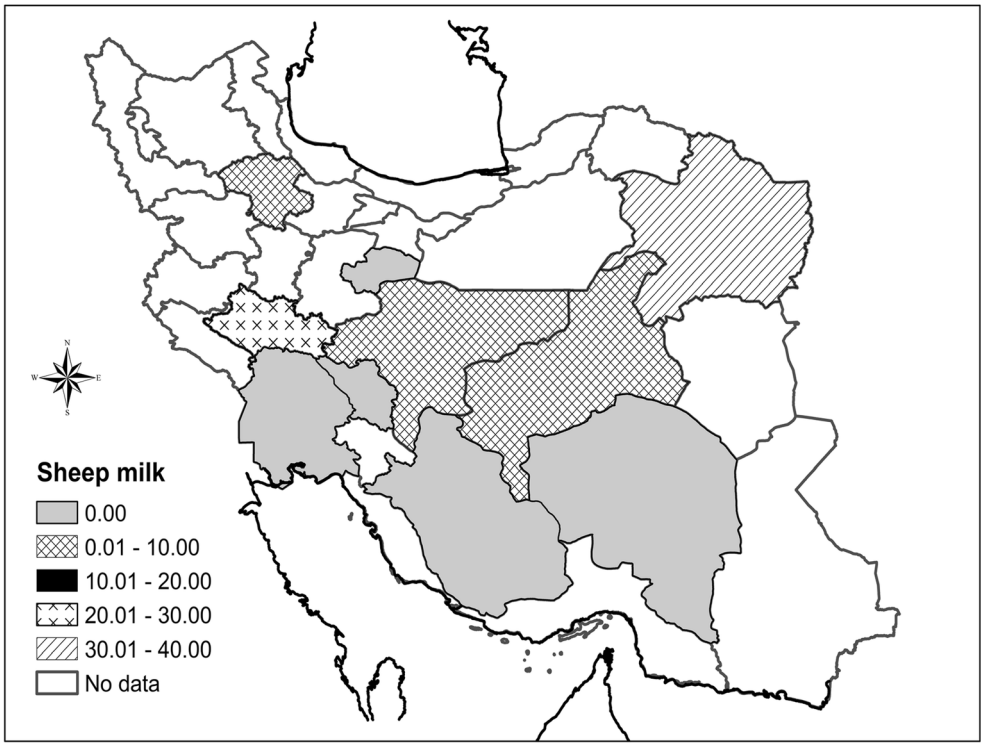

Fig. 7 Geographical distribution of C. *burnetti* in sheep milk by Arc GIS

31.97%, and 24.66% in cattle, goat, and sheep, respectively (Mobarez et al. 2017). The prevalence of *C. burnetii* in milk poses this bacterium as an important health risk in Iran.

Contamination of milk with *C. burnetii* can be dangerous to human through consumption of raw milk and unpasteurized dairy products (Gale et al. 2015). The hypothesis that consumption of dairy products from *C. burnetii*–infected animals may lead to foodborne Q fever in human is controversial (Angelakis and Raoult 2010). Some studies have reported higher seroprevalence and clinical disease in patients consuming raw milk (Eldin et al. 2013). Fortunately, this concern can be alleviated if contaminated milk is pasteurized. Currently, the target or index organism for pasteurization is *C. burnetii* (Cerf and Condron 2006). Unfortunately, the tradition of consuming dairy products made from unpasteurized milk, especially among those living in rural areas and remote regions, increases the risk of diseases caused by milk-borne pathogens. Therefore, it is necessary to take measures to raise awareness regarding prevention methods. On the other hand, contamination of raw milk can lead to generation of contaminated aerosols during various stages of milk manipulation, including milking of livestock and handling of milk at the farms and dairy factories, leading to the transmission of infection to humans. Therefore, it is necessary to take measures to raise awareness regarding preventive methods such as pasteurization of milk and use of personal protective equipment and appropriate containment when dealing with livestock.

In cattle, *C. burnetii* is shed by birth products, vaginal mucus, milk, and feces, urine, and semen (Guatteo et al. 2006). Contact with these contaminated materials can lead to human infection. Our results suggest that *C. burnetii* is highly prevalent in Iran (15.1%) in cow milk. In other countries, prevalence of *C. burnetii* showed different levels among cattle milk, for example, 4.7% in Switzerland (Fretz et al. 2007), 8.7% in Hungary (Gyuranecz et al. 2012), 18.8% in the Netherlands (Van Engelen et al. 2014), 22% in Egypt (Amin and Ahmed 2009), 14.3–40% in Italy (Petruzzelli et al. 2013), 28.9% in Saudi Arabia (Mohammed et al. 2014), 42.9% in the USA (Loftis et al. 2010), and 53.7% in Japan (Hirai et al. 2005). In our systematic review, the prevalence of *C. burnetii* varied in different geographical areas, the highest and lowest prevalence were seen in the East Azerbaijan (25.55%) and Khorasan-Razavi (4.22%) provinces, respectively. Also, *C. burnetii* was more prevalent in cow milk compared to goat and sheep milk in Iran. This result may reflect an increased prevalence of this pathogen in cattle, rather than in goats or sheep. Three million dairy cattle shed *C. burnetti* daily in the USA (Kim 2005). In Switzerland, 4.7% of bovine milk samples were positive for *C. burnetii* but all bovine and caprine milk samples were negative (Fretz et al. 2007). Therefore, shedding via milk in cows is one of the most common routes of spreading *C. burnetii* in the environment. This point should be taken into consideration in control measures of Q fever in animals.

Goats are another important source of *C. burnetii* infection in human. During recent outbreaks of Q fever in the Netherlands (more than 4000 human cases, 2007–2010) and Australia (2012–2014), human infections were mainly related

to dairy goat farming (Bond et al. 2016; Dijkstra et al. 2012). Based on our results, the investigation of *C. burnetii* in goat milk was conducted in 6 studies in 8 provinces. Prevalence in different geographical regions were highly variable with provinces of Qom (0%) and Lorestan (44.71%) showing the lowest and the highest frequency of *C. burnetii* in goat's milk, respectively. The pool estimated prevalence of *C. burnetii* in goat milk was 7.80% in Iran. Different prevalence of *C. burnetii* in goat milk were reported from others countries: 0% in Saudi Arabia (Mohammed et al. 2014), 0% in Switzerland (Fretz et al. 2007), 3.4% in Poland (Cisak et al. 2017), 14% in Egypt (Khalifa et al. 2016), and 32.9% in the Netherlands (Van den Brom et al. 2012). According to our previous study, goats (32%) had the highest seroprevalence of Q fever in Iran compared with cattle (11.5%) and sheep (23.7%) (Mobarez et al. 2017). Because it seems that goats are the main reservoir of human infection in Iran, but further studies are needed to prove this point, such as phylogenetic studies among *C. burnetii* from different animal and human sources.

Q fever outbreaks linked to infected sheep have been reported from around the world: Bulgaria, Croatia, France, Germany, Italy, and Switzerland (Van den Brom et al. 2015). Therefore, sheep is considered a main reservoir for human Q fever infection. Based on our results, the investigation of *C. burnetii* in sheep milk was conducted in 6 studies in 10 provinces of the Iran. *Coxiella burnetii* was detected in 5 provinces. Prevalence in different geographical regions was highly variable (0–34.8%). The highest frequency of *C. burnetii* in sheep's milk was detected in Khorasan-Razavi province (34.8%). The results of this meta-analysis showed that prevalence of *C. burnetii* was 3.79% in sheep milk. In other countries, the prevalence of *C. burnetii* differed among sheep milk, for example, 0% in Switzerland (Fretz et al. 2007), 0% in Saudi Arabia (Mohammed et al. 2014), 4% in Hungary (Gyuranecz et al. 2012), 6.5% in Turkey (Öngör et al. 2004), 17% in Egypt (Khalifa et al. 2016), and 22% in Spain (García-Pérez et al. 2009). According to our previous study, sheep (23.7%) had a high seroprevalence of Q fever in Iran (Mobarez et al. 2017), but *C. burnetii* had low prevalence in sheep milk. It should be noted that sheep shed the bacterium mostly in feces and vaginal mucus, in contrast with goats and cattle (shedding by milk) (Rodolakis et al. 2007). Most outbreaks of Q fever in humans in different parts of the world are related to sheep, so that of the 29 human Q fever outbreaks reported in Bulgaria, France, Germany, and the Netherlands (1982–2010), 17 outbreaks were associated with sheep (Georgiev et al. 2013; Van den Brom et al. 2015). It is very likely that different genotypes of *C. burnetii* are circulating in different hosts (goat, sheep, and cow) and therefore, molecular typing and genotyping studies are recommended to confirm the main source of human infections in Iran.

Finally, based on our results, the frequency of *C. burnetii* was 1.43% in camel milk. This prevalence in Iran was very low compared to other report, for example, 6.5% in Saudi Arabia (Mohammed et al. 2014). Because only one study has been done on this subject in Iran, it is very difficult to determine the overall prevalence of *C. burnetii* in camel milk. This subject must be further investigated in future studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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