PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Seroprevalence of Q fever among human and animal in Iran; A systematic review and meta-analysis

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Abstract

Background

Q fever is a main zoonotic disease around the world. The aim of this meta-analysis was to estimate the overall seroprevalence of *Coxiella burnetii* among human and animal population in Iran.

Methods

Major national and international databases were searched from 2005 up to August 2016. We extracted the prevalence of Q fever antibodies (IgG) as the main primary outcome. We reported the prevalence of the seropositivity as point and 95% confidence intervals.

Results

The overall seroprevalence of IgG phase I and II antibodies of Q fever in human was 19.80% (95% CI: 16.35–23.25%) and 32.86% (95% CI: 23.80–41.92%), respectively. The herd and individual prevalence of *C. burnetii* antibody in goat were 93.42% (95% CI: 80.23–100.00) and 31.97% (95% CI: 20.96–42.98%), respectively. The herd and individual prevalence of Q fever antibody in sheep's were 96.07% (95% CI: 89.11–100.00%) and 24.66% (95% CI: 19.81–29.51%), respectively. The herd and individual prevalence of *C. burnetii* antibody in cattle were 41.37% (95% CI: 17.88–64.86%) and 13.30% (95% CI: 2.98–23.62%), respectively. Individual seropositivity of Q fever in camel and dog were 28.26% (95% CI: 21.47–35.05) and 0.55% (0.03–2.68), respectively.

Conclusion

Seroprevalence of Q fever among human and domestic animals is considerable. Preventative planning and control of *C. burnetii* infections in Iran is necessary. Active surveillance and further research studies are recommended, to more clearly define the epidemiology and importance of *C. burnetii* infections in animals and people in Iran.

Author summary

Q fever is a zoonotic diseases caused by a bacterium so called *Coxiella burne*tii. Domestic ruminants (primarily cattle, sheep and goats) are the most important reservoir of *C. burnetii* in the nature. Q fever is mostly asymptomatic in livestock and animals. Clinical manifestations of Q fever in humans includes asymptomatic, acute, chronic to fatigue syndrome. Acute Q fever is defined as primary infection with *C. burnetii*, and <60% of infected patients may be asymptomatic. Acute Q fever can manifest as a flu-like and self-limited illness. Chronic Q fever is accompanied with endocarditis and vascular infection which is fatal if untreated. The results of this meta-analysis showed the prevalence of IgG phase I and II antibodies of *C. burnetii* among human in Iran were 19.80% and 32.86%, respectively. The prevalence of Q fever antibodies in cattle, goat and sheep were 13.30%, 31.97% and 24.66% in Iran, respectively. Seroprevalence of Q fever among human and domestic animals is considerable. Preventative planning and control of *C. burnetii* infections in Iran is necessary. Active surveillance and further research studies are recommended, to more clearly define the epidemiology and importance of *C. burnetii* infections in animals and people in Iran.

Introduction

Q fever is a zoonosis caused by the intracellular, gram negative bacterium *Coxiella burnetii*. *C. burnetii* is an extremely infectious pathogen [1]. The extremely high infectivity, the ability to withstand harsh environmental conditions, and the potential to cause severe disease in man, has deemed this organism to be considered as a biological terrorist agent. It has been listed as a Category B biological warfare agent by the Centre's of Disease Control and Prevention [2,3].

C. burnetii infects people and a wide range of wild and domesticated animals. Within the environment, *C. burnetii* survives in arthropod hosts, such as ticks. From these hosts it can spread, and it primarily spreads into ruminants. Domestic ruminants (primarily cattle, sheep and goats) are the most important reservoir of *C. burnetii* in the nature. Q fever is mostly asymptomatic in livestock and animals, except in some cases, where causes abortion, stillbirth, endometritis or infertility. Infected animals shed *C. burnetii* into the environment in milk, colostrum, urine, vaginal discharges and especially in birth products [4,5]. High numbers of organisms exist in the amniotic fluids and placenta during birthing (e.g., 10^9 bacteria/g placenta) [6]. *C. burnetii* can survive for long periods in the environment, and it is common for aerosols from infected herds to be carried by the wind and cause infection in humans. Q fever outbreaks could be directly connected to the speed and frequency of the wind [7]. Inhalation of infectious aerosol or contaminated dusts containing air-borne bacterium the major route of acquiring the disease in humans, so that a single inhaled organism may produce clinical illness. Nevertheless, the other routes of transmission of this infection to human are consumption of contaminated milks and dairy products, skin or mucosal contact, tick bites, blood transfusion, sexual transmission and embryo transfer [4,5,8].

Clinical manifestations of Q fever in humans includes acute, chronic to fatigue syndrome. The main characteristic of Q fever is its clinical polymorphism. Acute Q fever is defined as primary infection with *C. burnetii*, and <60% of infected patients may be asymptomatic [9]. However, acute Q fever can manifest as a flu-like and self-limited illness, and major clinical presentations of these patients are fever, headache, coughing, atypical pneumonia, hepatitis, myalgia, arthralgia, cardiac involvement, skin rash and neurologic signs, and 2% of patients

with acute disease are hospitalized. The case fatality rate of acute Q fever is reported up to 1–2% [4,8,10]. Approximately 5% of acute Q fever cases go on to develop chronic Q fever. People may become chronically infected without having being previously diagnosed with acute disease, and chronic Q fever may manifest months or years after an acute infection [11]. Chronic Q fever is accompanied with endocarditis, vascular infection, prosthetic joint arthritis, osteoarticular infection and lymphadenitis [4,12,13]. Endocarditis and vascular infection caused by Q fever are fatal if untreated[9].

Human Q fever has been described in countries around the world, New Zealand being the only exception. As it is not a notifiable disease in many countries, the geographical distribution of the organism is extrapolated from serological surveys and investigated outbreaks[3]. In Iran, the first clinical cases of acute Q fever are reported in 1952. From 1970 to 1976, 133 patients with acute Q fever were reported from different parts of Iran [14]. After 1976, Q fever was neglected in Iran, and no human case was reported. At the same time with large outbreak of Q fever in the Netherlands (2007–2010)[15],*C. burnetii* antibodies were reported in febrile patients in the Kerman province (southeastern Iran), [16]and investigation for Q fever was resumed. After that, various seroepidemiological studies were conducted on animal and human population. The first case of chronic Q fever (endocarditis) was reported in 2013 [17].

We do not have an overall estimation of Q fever infection in Iran. Current studies have reported Q fever seroprevalence in human and domestic animals. The overall estimation of Q fever seroprevalence in the human and animal population will help health policymakers create or modify control and prevention programs for Q fever in Iran. In the present systematic review, we reviewed the local Iranian publications on Q fever and also international publications relating to the disease in Iran. In this report we provide a summary of the more recent data collected on Q fever in Iran.

Methods

Information sources and search

From January 2005 to June 2016, we searched the literature for articles that assessed the prevalence of Q fever infection in human and animals in Iran.

We searched multiple English and Persian electronic data sources including Iranmedex, Scientific Information Database (SID), Magiran, Iranian Research Institute for Information Science and Technology (IRANDOC), Google Scholar, Medline, PubMed, Science Direct, Scopus and Web of science. In addition, the citations of the included articles 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. Keywords that we used for our search were "Q fever, *Coxiella burnetii* and Iran".

Eligibility criteria and study selection

Articles with cross sectional design which were sampling from Iran, published in Persian or English and measured seroposivity by serological assays (just IgG) were eligible to enter meta-analysis.

Exclusion criteria for studies from systematic review were: 1- Lack of access to full article or insufficient data in abstract; 2- Unclear testing methods used to detect studied infection or non-serology test 3- IgM detection4- other study design except cross sectional.

We contacted the corresponding author when we have questions about the eligibility of the article.

Data collection and data items

Data was extracted by two reviewers and checked twice based on the following items: type of study, sample size, location and time of the study, species and prevalence of Q fever. We grouped the studies with species in herd and individual level as sheep, goat, cattle and camel and also human participants as phase I and phase II IgG.

Analytic approach

We conducted meta-analyses in STATA version 12. We did meta-analysis for Q fever prevalence in any species in herd and individual level and in phase I and II for human. 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 pooled prevalence. Also by calculating pooled Q fever seroprevalence in each province we mapped prevalence of Q fever using ArcGIS ver. 10.2.

Results

Description of included studies

As presented in Fig 1, we found 163 abstracts in our literature review. After removing duplications (n = 87) based on title and abstract, 76 remained for full text review. Of those, 48 articles

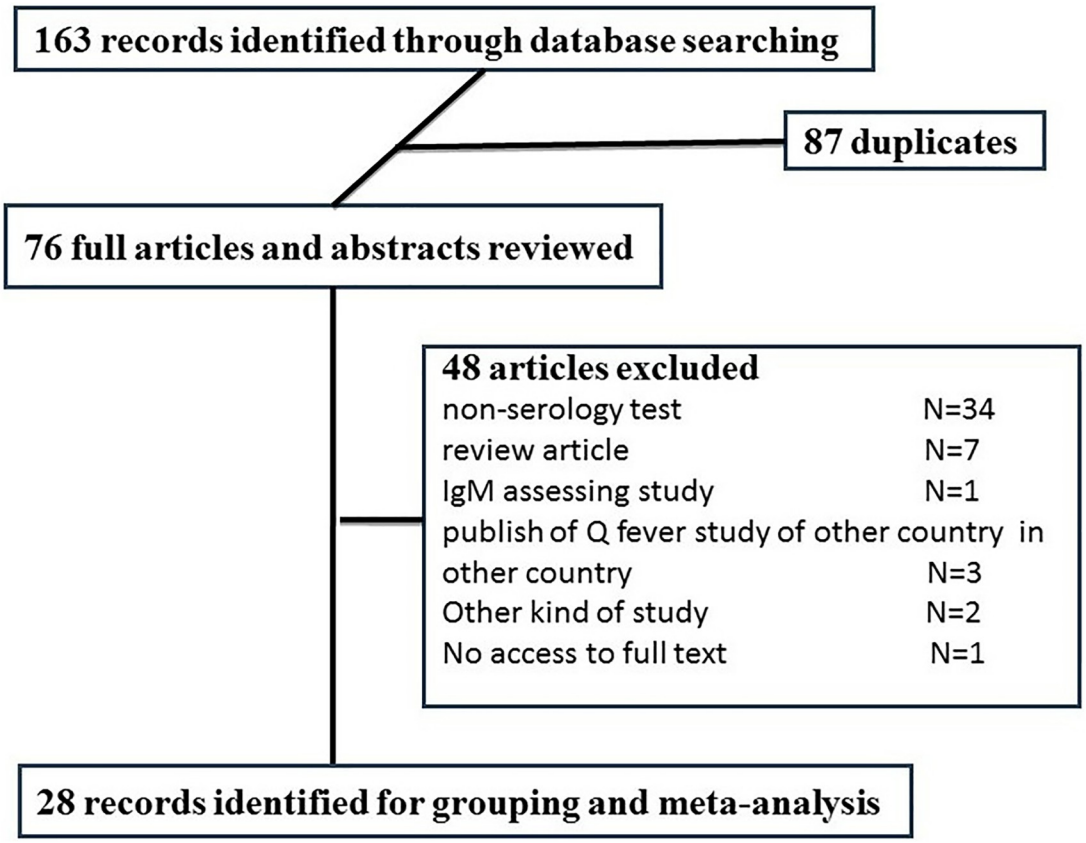

Fig 1. Flow diagram of included and excluded records

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were excluded for various reasons including non-serology test (n = 34), review article (n = 7), IgM assessing study (n = 1), publish of Q fever study of other country in Iranian journals (n = 3), other kind of study (n = 2) and no access to full text (n = 1) (Fig 1). Characteristics of the final included studies (n = 28) in the systematic review showed in Table 1.

Prevalence of seropositivity

Q fever seroprevalence in human. In final, 10 studies were found about seroprevalence of Q fever in different parts of Iran which three studies were about IgG phase I antibody and eighth studies were IgG phase II antibody. The overall seroprevalence of IgG phase I and II antibodies of Q fever in human was 19.80% (95% CI: 16.35–23.25%) and 32.86% (95% CI: 23.80–41.92%), respectively (Table 2). Geographical distribution of Q fever seropositivity was shown in Fig 2. *C. burnetii* antibodies have been detected in human from 9 provinces. The most prevalence of IgG phases I and II antibodies was seen in Kerman (24%) and South Khorasan (54%) provinces, respectively (Fig 2).

Q fever seroprevalence in goat. Six studies were conducted about seroprevalence of Q fever in goats which three studies were in herd level and six studies were in individual's level. The herd and individual prevalence of Q fever antibody in goat were 93.42% (95% CI: 80.23–100.00) and 31.97% (95% CI: 20.96–42.98%), respectively. The higher and lower seroprevalence was seen in Kerman (63.3%) and Markazi (0%) provinces, respectively. Also seroprevalence of Q fever among goats in Iran showed Fig 3.

Q fever seroprevalence in sheep. In final, 8 studies were found about seroprevalence of Q fever in sheep's, which 3 studies were in herd level and 9 studies were in individual's level. The herd and individual prevalence of Q fever antibody in sheep's were 96.07% (95% CI: 89.11–100.00%) and 24.66% (95% CI: 19.81–29.51%), respectively. The higher and lower seropositivity of *C. burnetii* among sheep's showed in Sistan va Baluchestan (43.6%) and Khorasan Razavi (12.8%) provinces, respectively. Also geographical distribution of Q fever seropositivity in sheep's was shown in Fig 4.

Q fever seroprevalence in cattle. In final, 8 studies had been done about seroprevalence of Q fever in sheep's, which 7 studies were in herd level and 5 studies were in individual's level. The herd and individual prevalence of Q fever antibody in cattle were 41.37% (95% CI: 17.88–64.86%) and 13.30% (95% CI: 2.98–23.62%), respectively. The seroprevalence of Q fever among cattle's in the different parts of Iran showed in Fig 5.

Other animals. Only one study found the seroprevalence of dogs and camels in Iran. Individual seropositivity of Q fever in camel and dog were 28.26% (95% CI: 21.47–35.05) and 0.55% (0.03–2.68), respectively.

Discussion

The current systematic review reports the seroprevalence of Q fever among human and domestic animals in Iran. The results of this meta-analysis showed the prevalence of IgG phase I and II antibodies of *C. burnetii* among human in Iran were 19.80% and 32.86%, respectively. These rates were very high compared with other similar study. As example seropositivity of Q fever in China was reported 10% [18]. In a recent systematic review study, human seroprevalence was reported from 1–32% in Africa [19]. Human seroprevalence of Q fever were reported 3 to 35.8% in Kenya [20], 12.3–32%in Turkey[21,22], 15.3% in Spain [23],5.2%in Australia[24]and 11% in Denmark[25]. Overall seroprevalence for *C. burnetii* was reported 3.1% among general population in the USA [26]. The differences between countries could be due to varieties in ecologic, social, cultural, behavioral and economical conditions and also levels of animals infections, which affect the exposures of people in each of the regions of the

Table 1. Characteristics of the included studies in the systematic review, 2005–2016.

	Group	Level	Sample Size	Time Study	Province	Reference
1	Human	Phase I	187	2011	Sistan and Baluchistan	[44]
		Phase II				
2	Human	Phase I	75	2009	Kerman	[16]
		Phase II				
3	Human	Phase I	250	2011–2012	Kurdistan	[45]
		Phase II				
4	Human	Phase II	200	2014	Ardabil	[46]
					Khuzestan	
5	Human	Phase II	105	2011	Sistan v Baluchistan	[47]
6	Human	Phase II	45	2013	Kerman	[48]
7	Human	Phase II	75	2010–2011	Kerman	[49]
8	Human	Phase II	121	2014	Kerman	[50]
9	Human	Phase II	53	2015–2016	Mazandaran	[51]
10	Human	Phase II	92	2014	South Khorasan	[52]
11	Sheep	Herd	10	2009	Kerman	[53]
		Individual	85			
12	Sheep	Herd	29	2012	Khorasan Razavi	[54]
		Individual	255			
13	Sheep	Herd	10	2014	Hamadan	[41]
		Individual	200			
14	Sheep	Individual	256	2011–2012	Ardabil	[55]
15	Sheep	Individual	235	2011–2012	Fars	[34]
			336		Isfahan	
			297		Khorasan Razavi	
			232		Markazi	
16	Sheep	Individual	12	2011	Hormozgan	[35]
			37	2011	Kerman	
			78	2011	Sistan v Baluchistan	
17	Sheep	Individual	220	2010–2011	Khuzestan	[56]
18	Sheep	Individual	253	2011–2012	Mazandaran	[57]
19	Goat	Herd	9	2008	Kerman	[58]
		Individual	79			
20	Goat	Herd	28	2012	Khorasan Razavi	[54]
		Individual	205			
21	Goat	Herd	10	2014	Hamadan	[41]
		Individual	50			
22	Goat	Individual	76	2011–2012	Fars	[34]
			76		Isfahan	
			13		Khorasan Razavi	
			15		Markazi	
23	Goat	Individual	58	2011	Kerman	[59]
24	Goat	Individual	39	2011	Hormozgan	[35]
			136		Kerman	
			66		Sistan v Baluchistan	
25	Cattle	Herd	10	2014	Hamedan	[41]
		Individual	120			

(*Continued*)

Table 1. (*Continued*)

	Group	Level	Sample Size	Time Study	Province	Reference
26	Cattle	Herd	12	2008	Kerman	[58]
		Individual	93			
27	Cattle	Herd	44	2010	Kerman	[60]
28	Cattle	Herd	19	2011	Kerman	[40]
		Individual	161			
29	Cattle	Herd	19	2010	Khorasan Razavi	[61]
		Individual	246			
30	Cattle	Herd	34	2014	Kurdistan	[62]
31	Cattle	Herd	37	2014	West Azerbaijan	[63]
32	Cattle	Individual	86	2011	Khuzestan	[64]
33	Camel	Individual	42	2012–2013	Khorasan Razavi	[65]
			59		North Khorasan	
			66		South Khorasan	
34	Dog	Individual	182	2013–2014	Khuzestan	[66]

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world. In all conducted studies in Iran, *C. burnetii* antibodies have been detected in human from 9 provinces. Seroprevalence varied in different areas of Iran. The seroprevalence of IgG phase I of Q fever ranged from 18.2% to 24%, which Sistan and Baluchestan and Kerman provinces had lowest and highest seropositivity, respectively. Also the prevalence of IgG phase II antibodies ranged from 14.5% to 68%, which higher and lower seroprevalence showed in Kerman and Sistan and Baluchestan provinces, respectively [17,18]. According to the findings of this study, it is highly recommended that physicians and health care workers are informed about bacteria circulating in Iran.

Goats are important sources of *C. burnetii* infection in people and seven serosurveys were conducted on goats in Iran between 2005 and 2016. According to the results of this meta-analysis, the seroprevalence of Q fever in goats was 31.97%. Also, 93.42% of the goat's herds were seropositive in Iran. In similar studies, goats seropositivity were 13% to 23% in Africa [19],20% to 46% in Kenya [20] and 0.8% to 60.6% in China [18]. Antibodies against *C. burnetii* in Netherland, Bulgaria and Bangladesh were 7.8%, 13.7% and 9.52%, respectively [27–29]. Our study showed *C. burnetii* antibodies have been detected in goats from 7 provinces. The higher and lower seroprevalence was seen in Kerman (65.8%) and Markazi (0%) provinces, respectively. From 2007 to 2010, more than 4,000 human cases were diagnosed in Netherlands. The outbreaks

Table 2. Prevalence Q fever antibody among human and domestic animals, 2005–2016

	Level	Sample size	Number of studies	Pooled estimate (%)
Human	Phase I	512	3	19.80 (16.35–23.25)
	Phase II	1203	10	32.86 (23.80–41.92)
Goat	Herd	47	3	93.42(80.23–100.00)
	Individual	813	6	31.97 (20.96–42.98)
Sheep	Herd	49	3	96.07 (89.11–100.00)
	Individual	2496	9	24.66 (19.81–29.51)
Cattle	Herd	175	7	41.37 (17.88–64.86)
	Individual	706	5	13.30 (2.98–23.62)
Camel	Individual	167	1	28.26 (21.47–35.05)
Dog	Individual	182	1	0.55 (0.03–2.68)

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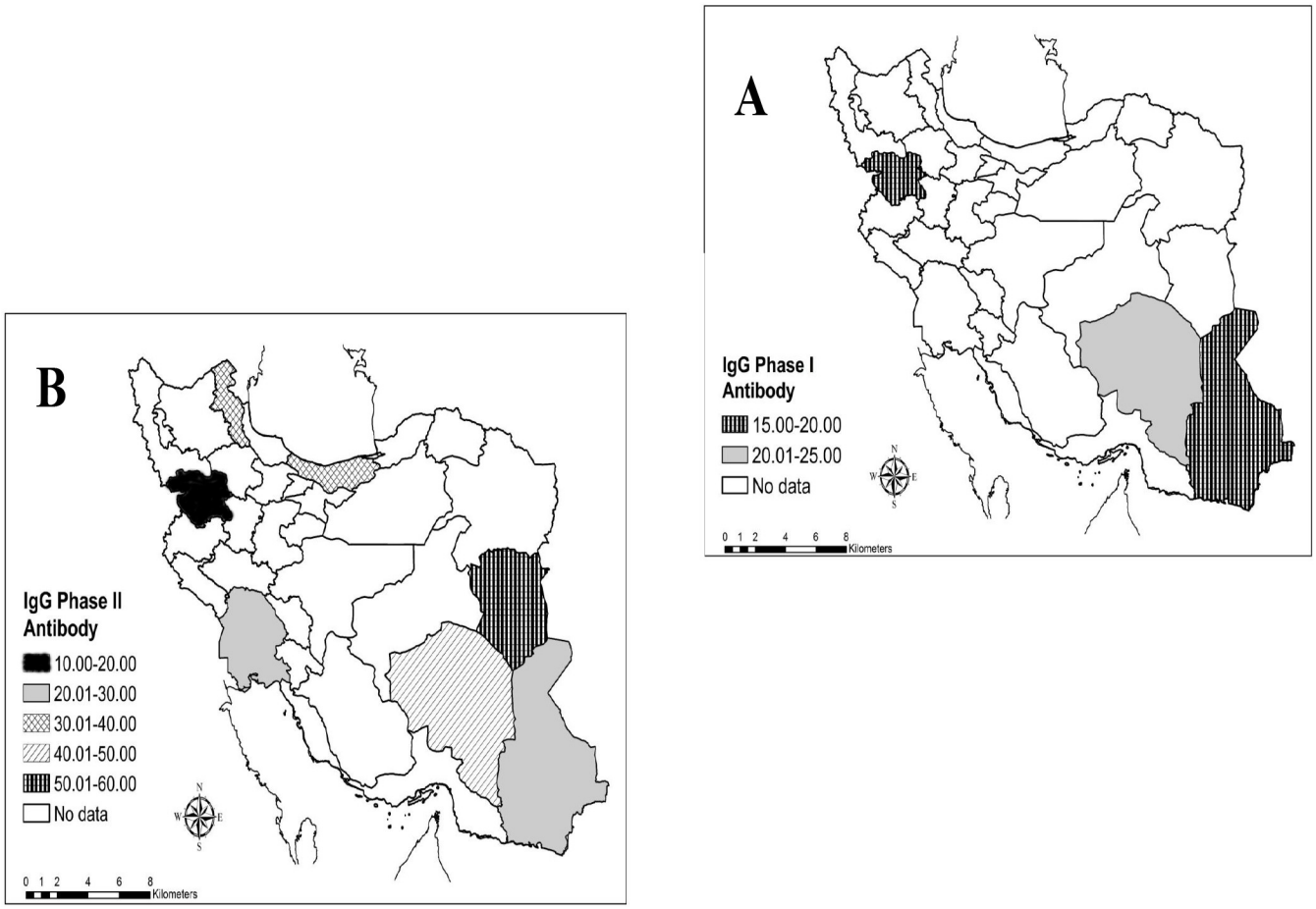

Fig 2. Geographical distribution of anti- *C. burnetii* IgG Phase I (A) and IgG Phase II (B) among Iranian people.

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in humans were mainly related area with intensive dairy goat farming [15]. A recent (2012–2014) human outbreak of Q fever in the Australia was linked to an intensive goat and sheep dairy farm and also seroprevalence in goats was 15% [30]. Due to the recent outbreaks of Q fever, it seems that the goat is very strong role in human infections. In Iran, due to the high seroprevalence antibodies to *C. burnetii* in goats, this case can be possible, but more studies are needed to prove this point in the future.

Large human Q fever outbreaks related to sheep in published studies around the world included Bulgaria (2009), Croatia (2008),France (2007), Germany (2006, 2008), Italy (2004) and Switzerland (1987) [31]. Therefore, sheep is considered as an important factor for human Q fever infection. The results of this meta-analysis demonstrated that were 24.66% of sheep's had antibody of *C. burnetii* in Iran. In total, seroprevalence of Q fever was 96.07% among sheep's herds. Different rates of sheep seroprevalence were reported in other countries, so that the seropositivity was 2.4% in Netherlands [32], 5% in China [18], 11.6% in Bulgaria [28], 20% in Turkey [33] and 11% to 33% in Africa [19]. The studies of Q fever seroprevalence found in 12 provinces in Iran. The higher and lower seropositivity of *C. burnetii* among sheep's showed in Sistan and Baluchestan (43.6%) and Khorasan Razavi (12.8%) provinces, respectively [34,35].

In cattle's like other main reservoirs (sheep and goat) of Q fever, *C. burnetii* is shed by birth products (placenta, birth fluids), but may also be shed by vaginal mucus, milk, and faeces,

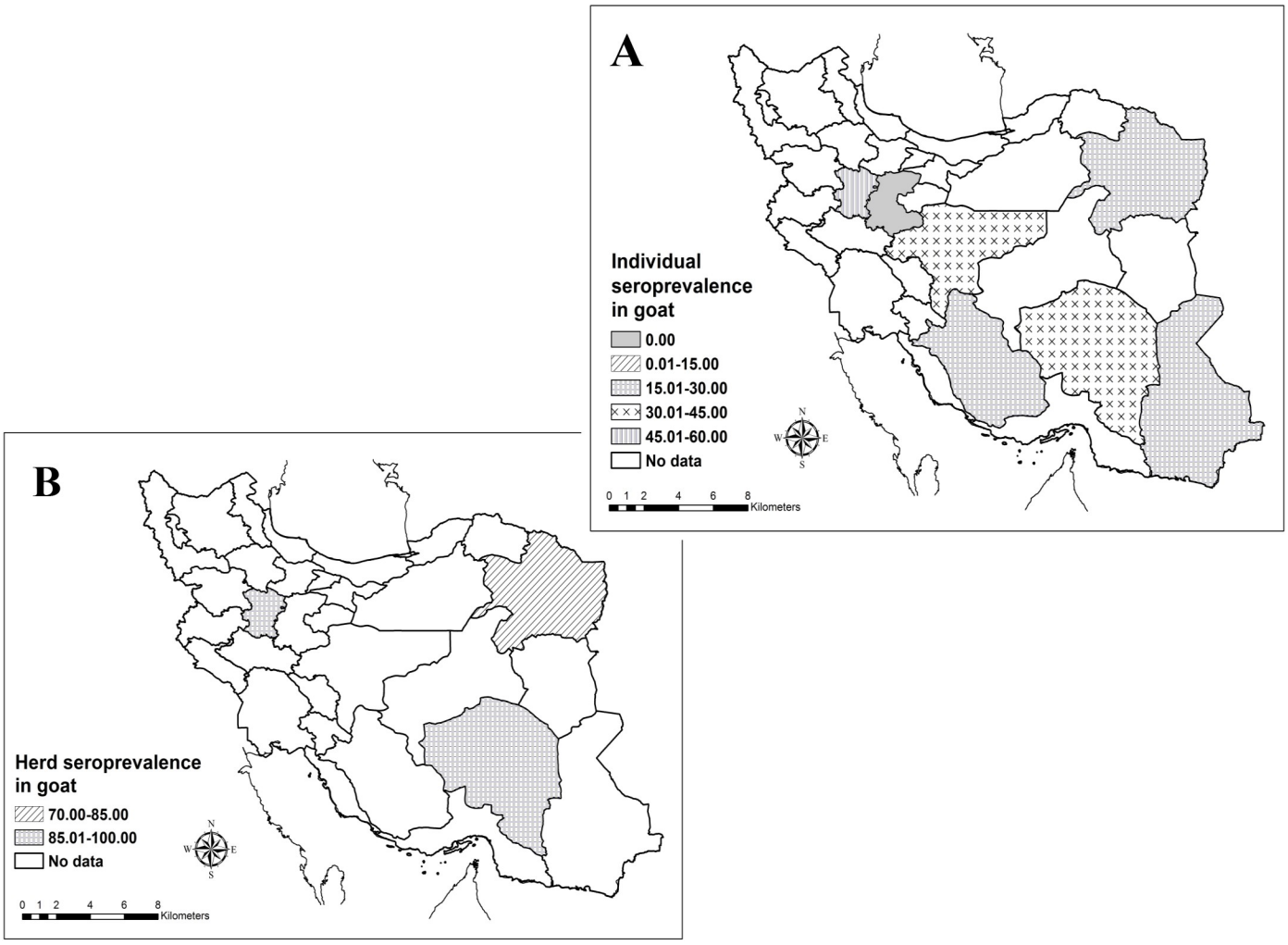

Fig 3. Geographical distribution of Q fever seropositivity among goats in individual (A) and herd (B) levels in the Iran.

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urine and semen[36].Contact with these contaminated materials can lead to human infection. According to the results of this meta-analysis, the seroprevalence of Q fever in cattle was 13.30%. Also, 41.37% of the cattle's herds were seropositive in Iran. In other countries, seroprevalence of Q fever was different rates among cattle, for example: 6.2% in Northern Ireland [37], 8.5% in in Bulgaria [28], 15% in China [18], 16.0% in Netherlands [38] and 30.4% in Cameroon [39]. In all conducted studies in Iran, *C. burnetii* antibodies have been detected in human from 7 provinces. The higher and lower seroprevalence of Q fever was seen in Kerman (29.2%) and Hamadan (0.8%) provinces, respectively[40,41]. The lower seroprevalence in cattle's compared to the two other main reservoirs (sheep and goat) in Iran, this can be caused by difference in strains circulating in Iran and other areas and genotyping studies can be helpful in support of this subject. Therefore, it seems that there are differences in geographic prevalence of the disease among cattle in Iran and it is recommended to be done in the future a comprehensive study to determine the case in all provinces of Iran.

The seropositivity of Q fever among camel was 28.26% in Iran. Antibodies to *C. burnetii* were reported in 51.6% and 80% of camels in Saudi Arabia and Chad, respectively [42,43].

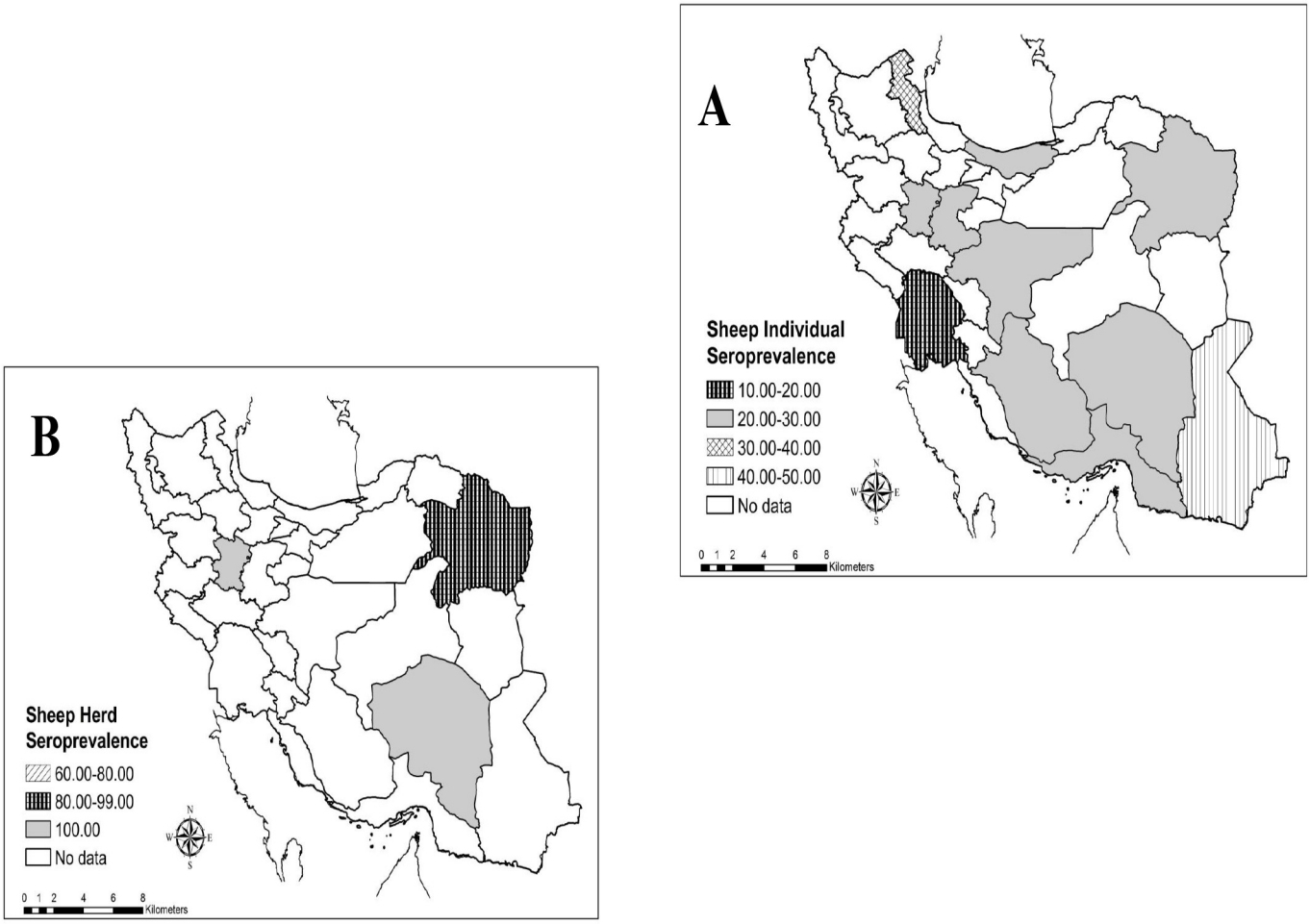

Fig 4. Geographical distribution of *C. burnetii* seroprevalence among sheep's in individual (A) and herd (B) levels in Iran.

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Also, the seroprevalence of Q fever was 0.55% among dogs in Iran, but only one study conducted in Iran. For better judgment on this issue needs more studies in the future.

Although human and animal infections of Q fever are known to occur and endemic in Iran, but the Q fever is not a reportable disease in the country and clinical cases are probably largely unrecognizable by health system. There is a need for information on the epidemiology of *C. burnetii* in Iran as well as many other issues such as distribution, pathogenesis and molecular typing. The data from the studies to date in Iran provide only a basic picture of Q fever in the country. Active case finding and further research studies are recommended, to more clearly define the epidemiology and importance of *C. burnetii* infections in animals and people in Iran. This will enable the formulation and implementation of locally applicable control methods for Q fever which can be implemented by animal and human healthcare workers.

Ethical approval

Not applicable.

Informed consent

Not applicable.

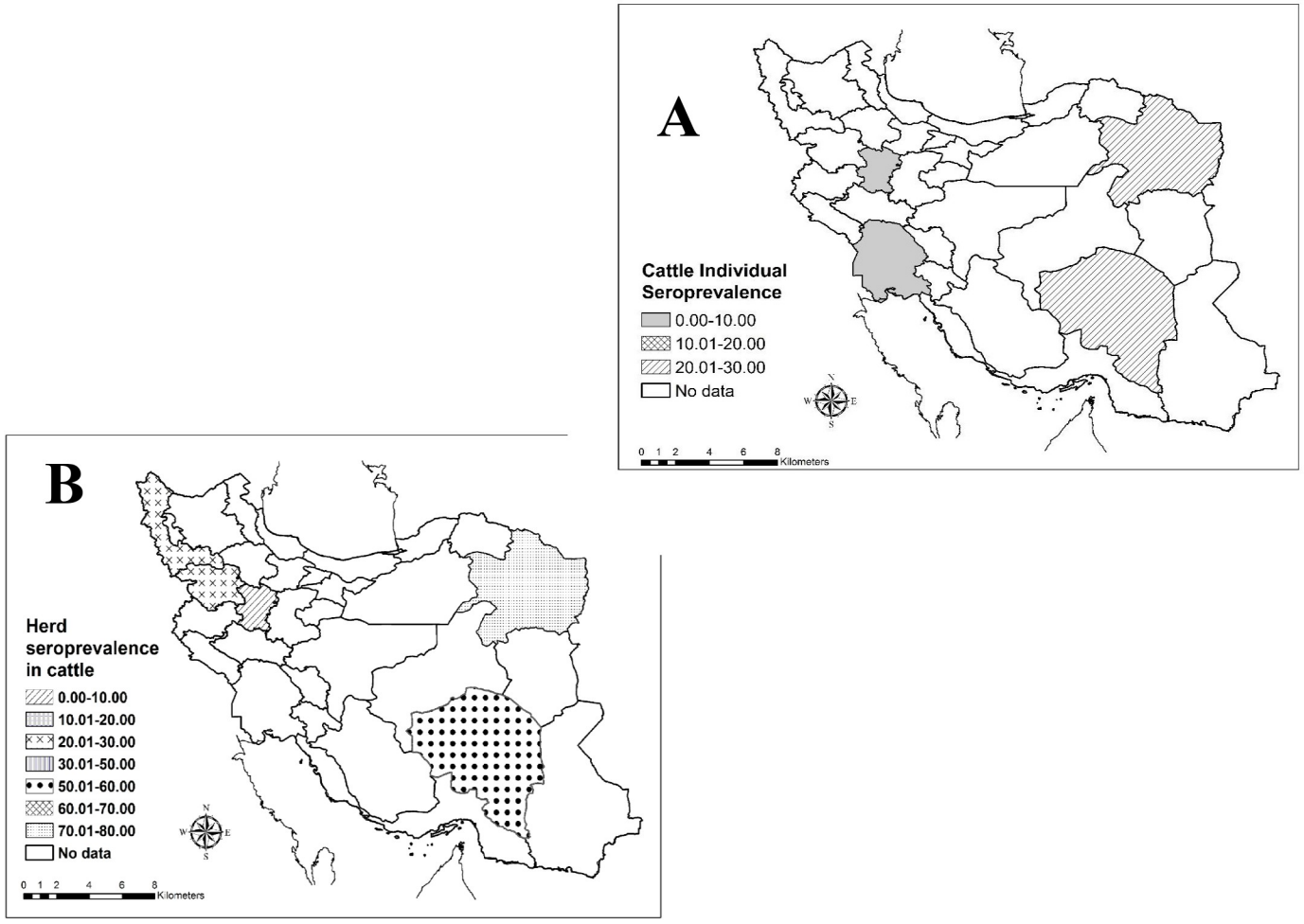

Fig 5. Geographical distribution of Q fever seropositivity among cattle's in individual (A) and herd (B) levels in Iran.

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Supporting information

S1 Fig. PRISMA 2009 Flow Diagram.
(PDF)

S1 Table. PRISMA 2009 Checklist.
(DOC)

Author Contributions

Conceptualization: SE AMM.

Data curation: SE AMM FBA.

Formal analysis: FBA.

Funding acquisition: SE.

Investigation: SE AMM FBA.

Methodology: SE AMM FBA.

Project administration: SE AMM.

Resources: SE AMM FBA.

Software: SE FBA.

Supervision: SE AMM.

Validation: SE FBA.

Visualization: SE AMM FBA.

Writing – original draft: SE.

Writing – review & editing: SE AMM FBA.

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