Asian Journal of Epidemiology 5 (3): 66-74, 2012
ISSN 1992-1462 / DOI: 10.3923/aje.2012.66.74

Q Fever: An Emerging Public Health Concern in Iran

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ABSTRACT

Q fever is a zoonotic disease considered as an emerging or re-emerging disease in many countries. It is caused by *Coxiella burnetii* that are highly resistant to the environment. The most common reservoirs of the diseases are livestock. In this study, all studies carried out on Q fever in Iran were reviewed, in order to have a better understanding of the epidemiological features of the disease in this country. All published documents were systematically searched to find the related studies between the years 1937 and 2012. The collected studies were then classified based on the study group. In this review 29 published papers or reports were found, which included 12 studies on animals and birds, 1 on foetuses, 4 on ticks, 4 on milk and 14 on humans. The existence of the Q fever pathogen has been confirmed in different molecular and serological studies among different animals (including sheep, cattle, goats, horses, camels, wild rodents and wild pigeons) and their productions in Iran. Also, there are few seroepidemiological studies on the presence of human Q fever in Iran that most of them confirmed this issue. According to this study, Iran can be considered as an endemic focus of Q fever. As the presence of *C. burnetii* or its antibody has been reported among different animals in Iran, the disease can be transmitted to humans and so it can be considered as a public health problem in Iran.

Key words: *Coxiella burnetii*, prevalence, Iran, animal, human, GIS

INTRODUCTION

Q fever is a zoonotic disease caused by a rickettsia called *Coxiella burnetii* (Maurin and Raoult, 1999). Domestic animals and pets are the main reservoirs of infection and transmission to human beings is mainly accomplished through inhalation of dust or aerosols contaminated with amniotic fluid, placenta material or excreta from infected animals (Angelakis and Raoult, 2010). *C. burnetii* can survive for a long period in the inanimate environment. These can lead to the production of secondary aerosols, which, it is suggested, are a major factor in the spread of the pathogen and have been postulated as the typical cause of outbreaks in humans. The dust in the wind can carry the organism and as little as one pathogen can cause human disease (Hawker *et al*., 1998; Leski *et al*., 2011).

The illness in humans is associated with a wide clinical spectrum, from asymptomatic or mildly symptomatic seroconversion to fatal disease (Angelakis and Raoult, 2010). It can manifest as an acute disease (mainly as a self-limited febrile illness, pneumonia, or hepatitis) or as a chronic disease (mainly endocarditis), especially in patients with previous valvulopathy and to a lesser

extent in immuno-compromised hosts. In animals, in contrast, infection is mainly subclinical, but has been associated with late abortions, stillbirth, delivery of weak offspring and also infertility (Norlander, 2000).

Q fever has been reported worldwide. The disease has recently been reported in countries neighbouring Iran, including Oman in 2000 (Scrimgeour *et al.*, 2003), Iraq in 2003 (Leung-Shea and Danaher, 2006), Afghanistan in 2006 (Bailey *et al.*, 2011), United Arab Emirates in 2008 (Lloyd *et al.*, 2010), Turkey in 2010 (Karabay *et al.*, 2011) and Saudi Arabia in 2011 (Hussein *et al.*, 2012).

The disease can be endemic in domestic animals in regions with no reports of human cases, i.e., in the Netherlands; Q fever had been endemic in dairy goats, sheep and cattle for more than forty years before the outbreak in humans in 2007-2009, which affected 3523 patients (Norlander, 2000; Roest *et al.*, 2011).

In this study all studies carried out on Q fever in Iran were reviewed, in order to have a better understanding of the epidemiological features of the disease in this country.

SEARCH STRATEGY

To find relevant studies, Medline (PubMed), ISI Web of knowledge, Science Direct, Embase and Scopus were systematically searched for publications from 1937 (time of discovery of pathogen) to May 2012 relating to Q fever in Iran. In addition, Iranian search engines such as Scientific Information Database, (SID), Medlib, Magiran and IranMedex were searched for related Persian papers. In order to maximize the sensitivity of the search, general keywords such as "Coxiella" or "Rickettsia" or "Q fever" and "Iran" were co-searched. Finally, with the help of Google Scholar, all relevant papers and reports that were not found in any of the previous databases were collected.

Moreover, in order to maximize the sensitivity of the search, bibliographies of identified studies were screened for additional relevant studies. All the resultant titles and abstracts for the disease were reviewed. The full texts of all relevant articles were then assessed by reviewers. Studies were included if they provided information of Q fever or *Coxiella burnetii* in English, French or Persian languages. Unrelated studies were then excluded. The collected studies were then classified based on the study group (animals and birds, foetuses, ticks, milk and humans) and sorted according to the time of the study. The locations of the study areas were then illustrated using a GIS based map.

In this review 29 published papers or reports were found, which included 12 studies on animals and birds, 1 on foetuses, 4 on ticks, 4 on milk and 14 on humans. Some of these reports covered more than one of the aforementioned categories.

PREVALENCE OF DISEASE

Animal and bird sera: In 1956, in a wide serological survey of animals, evidence of the disease was found over a large area (location not determined) (Caughey and Harootunian, 1976).

In 1973-1975, in three different serological studies, evidence of the disease was shown in the sera of different domestic animals, small mammals and wild rodents in Iran (location not determined) (Saadatezadeh *et al.*, 1973; Hamidi *et al.*, 1974; Saadatezadeh, 1976).

In 1988, the Q fever studies restarted and 7.9% of 152 wild city pigeons in Tehran, north of Iran, were seropositive for *C. burnetii* (Bashiribod, 1989).

There was no evidence of *C. burnetii* in blood samples of sheep, cattle, goats, dogs and hedgehogs that were tested by the Nested PCR method in Mazandaran, north of Iran in 2003 (Bashiribod *et al.*, 2008).

In 2009, 35.5% of 169 caprine and bovine sera from southeast Iran were seropositive for Q fever. Goats had a significantly higher average seroprevalence (65.78%) than cattle (10.75%) (Khalili and Sakhaee, 2009). In this year, in another study, antibodies were detected in 29.42% of 85 sheep sera samples collected in southeast Iran (Sakhaee and Khalili, 2010).

In 2010, 22.3% of 246 dairy cattle in Khorasan Razavi province, in eastern Iran, were seropositive for Q fever (Azizzadeh *et al*., 2011). In this year, the seropositivity with Q fever was 23.7% in 253 collected sheep sera from Mazandaran in north of Iran (Mostafavi *et al*., 2012).

In a recent study, more than 20 percent of 190 tested sheep were seropositive for Q fever in Ardebil, northwest Iran (unpublished data).

As the studies carried out on birds and their products is limited to two studies, further research on the possible dangers of poultry products are required to elucidate the epidemiology of Q fever in Iran.

Animal foetuses: *C. burnetii* is a potent candidate for domestic animal abortion in Iran. In 2010, *C. burnetii* was detected in ovine and caprine aborted foetuses in ten provinces of different parts of the country including Isfahan, Khuzestan, Golestan, Gilan, Khorasan, Kerman, Fars, Kurdistan, Ilam and Sistan and Baluchistan using PCR methods (Dehkordi, 2011). Even though this study has shown that a high percentage of ovine and caprine aborted foetuses were positive for the presence of *Coxiella burnetii* by nested PCR, the validity and quality of this study and its techniques need further evaluation. Bases on these findings, infected fatal fluids and membranes, aborted foetuses and contaminated bedding should be incinerated or buried.

Milk samples: In 2008, in Chaharmahal and Bakhtiari province, in western Iran, 6.2% of bovine bulk milk samples, 1.8% of caprine bulk milk samples and 0% of ovine bulk milk samples from 376 bulk milk samples were positive for *C. burnetii* by trans-PCR method (Rahimi *et al*., 2011).

In 2009, anti *C. burnetii* antibodies were detected in 45.4% of bulk milk samples from 44 large commercial dairy herds in Kerman, southeast Iran (Khalili *et al*., 2011).

In 2010, in a study in Isfahan province, central Iran, 5.7, 4.5, 3.2 and 1.4% of ovine, caprine, bovine and camel bulk milk samples from 567 bulk milk samples were positive for *C. burnetii* (Rahimi *et al*., 2010).

In 2010, 18.2, 4.2 and 5.5% of 220 goat bulk milk samples from Fars, Khuzestan and Yazd provinces were positive, but all 76 goat bulk milk samples from Qom and Kerman provinces were negative (Rahimi, 2010).

In 2012, in a study in Jahrom city, southern Iran, 11% of 100 bovine bulk milk samples tested by nested PCR were positive for the presence of *C. burnetii* (Kargar *et al*., 2012).

The results of studies carried out on the milk of clinically healthy dairy cattle herds and detection of *C. burnetii* in most of the tested bulk tank samples indicates that these products can be another source of *C. burnetii* infection for humans in Iran, although ingestion (mainly drinking unpasteurized milk) is probably a minor cause of outbreaks (Hung *et al*., 2010).

Eggs: In 2010, in a study carried out in Isfahan province, central Iran and Gilan and Mazandaran provinces, northern Iran, 1.5% of 130 hen egg samples and 7.7% of 104 duck egg samples were positive and 34 goose, 70 quail and 31 ostrich egg samples were negative for *C. burnetii* (Rahimi and Doosti, 2012).

Ticks: In 1951, Q fever was detected in ticks collected from domestic animals in Kermanshah, western Iran (Rafyi and Maghani, 1954).

In 1954, ticks collected from Sabzevar, eastern Iran, showed evidence of infection with *C. burnetii* (Kaplan and Bertagna, 1955; Dean, 1957).

In 1975, 10% of 1450 ticks collected from different locations in Iran, were positive for C. *burnetii* and one strain of *C. burnetii* was isolated for the first time in Iran (location not determined) (Saadatezadeh, 1976).

After 28 years gap in Q fever studies, in a study in 2003, there was no evidence of *C. burnetii* in 605 hard ticks from Mazandaran, northern Iran (Bashiribod *et al*., 2008).

In 2009, out of a total of 160 ticks collected from domestic animals in Kerman province, southeast Iran, three pools consisting of 5 *Hyalomma anatolicum anatolicum* and one pool of three *Rhipicephalus sanguineus* ticks collected on goats and sheep were found to be positive using Trans-PCR (Fard and Khalili, 2011).

Humans: Although the existence of the Q fever pathogen has been confirmed in different molecular and serological studies in Iran, nevertheless it would seem that this disease has been neglected by the national health system and subsequently there have been no reports of human cases in Iran since 1976.

The first human case of Q fever in Iran dates back to 1952 (Giroud and Yassemi, 1995). In this year, two human subjects in Abadan, southwest of Iran, were reported to be positive for Q fever (Courdurier *et al*., 1952). Two years later, in 1954, evidence of the existence of the disease in human subjects was reported in villages in the region of Sabzevar in eastern Iran. 20 (46.5%) of the 43 villages tested had serum positive humans (Kaplan and Bertagna, 1955; Dean, 1957).

In 1954, Q fever was reported in serum samples from Nardine, northeast Iran; Taibad, in eastern Iran on the Afghan frontier (Gadjusek and Bahmanyar, 1955) and in Sirjan, in southern Iran (Dean, 1957) using serological tests.

In 1956, in a wide serological survey in humans, evidence of the disease was found over a large area of the country (study area not determined) (Caughey and Harootunian, 1976).

In 1970, some clinical cases were reported from Shiraz (Eghtedari *et al*., 1970) and in 1971 the disease was reported among Dutch expatriates in Iran (study area not determined) (Caughey *et al*., 1971).

In 1973, a serological study showed evidence of the disease in the sera of humans in Iran (study area not determined) (Saadatezadeh *et al*., 1973).

Between 1970 and 1973, 49 acute cases were diagnosed in Abadan, south western Iran (Caughey and Harootunian, 1976) and between 1972-1976, 80 patients were diagnosed clinically and serologically in southern Iran (Caughey, 1977).

In 1975, in a study of different locations in Iran 11% of humans were seropositive (study area not determined) (Saadatezadeh, 1976).

In 1991, 27.5% of forty human sera examined for the presence of antibodies to *C. burnetii* by ELISA and IFA test were positive (the study area is not determined) (Kovacova *et al*., 1996).

In 1974, 8.3% of 252 Iranians and 44% of 64 foreigner expatriates were confirmed to be Q fever seropositive (location not determined) (Caughey and Harootunian, 1976).

In 1975, 13.5% of 318 tested persons were seropositive for Q fever (location not determined) (Caughey and Harootunian, 1976).

In 2003, all of 120 human samples were negative for *C. burnetii* in 120 human samples collected from western Mazandaran, in the north of Iran (Bashiribod *et al*., 2008).

In 2009, in 75 febrile patients in Bardsir, southeast Iran 24 and 36 % had phases I and II specific *C. burnetii* IgG antibodies, respectively (Khalili *et al.*, 2010).

Because of the complications of differential diagnosis of Q fever in its acute and chronic form with other infectious diseases, its extremely low fatality rate, restricted confirmed reports of the outbreaks and limited educational plans for physicians and specialists, Q fever attracts relatively little attention from public health workers in most countries including Iran. On the other hand, in countries such as France and the Netherlands, where high levels of the acute and chronic form of the disease are reported, this reflects a high level of national awareness of the disease (Fournier *et al.*, 1996).

The high prevalence of antibodies compared with relatively few reports of clinical cases leads to the speculation that many cases are misdiagnosed, unrecognized or are subclinical and it is expected that higher numbers of human cases of the disease will be found if the case reporting system of the disease in humans is more sensitive and the awareness of physicians about the disease is increased. So, further studies are recommended to diagnose the acute and chronic Q fever cases in Iran.

As Q fever is recognized as an occupational disease in most parts of the world, Iranian farmers, dairy workers, butchers, meat packers and laboratory workers should be informed about Q fever risk factors and signs.

For humans, grey shaded figures point to clinically confirmed cases and grey shapes the seropositive cases.

DISCUSSION

From these findings, Iran can be considered as an endemic focus of Q fever, where domestic animals play an important role in the spread of the disease. As the presence of *C. burnetii* or its antibody has been reported among different animals (including sheep, cattle, goats, horses, camels, wild rodents and wild pigeons) in Iran (Fig. 1), the disease can be transmitted to humans and so it can be considered a public health problem in Iran like many other countries such as France, the United Kingdom, Italy, Spain, Germany, Greece and Canada where the disease has been reported in humans after reports of it already existing in animals (Hartzell *et al.*, 2008; Angelakis and Raoult, 2010).

There are few seroepidemiological studies on human Q fever in Iran. As in other countries, in Iran, Q fever is primarily an occupational hazard in those persons in close contact with domestic animals and dairy products, such as farmers, veterinarians and slaughterhouse workers. Laboratory personnel and health care workers are also at risk of Q fever infection.

Q fever can also be linked to the inhalation of desert dust. Desert areas of Iraq are among the largest sources of airborne dust on the earth (Washington *et al.*, 2003). Due to the fact that in recent years the heavy dust storms originating from Iraq have hit the western and south-western provinces of Iran, that the presence of *C. burnetii* has been confirmed in these particles (Leski *et al.*, 2011) and that this pathogen is known to persist for long periods in the environment (Maurin and Raoult, 1999); the human population in these provinces may also be at risk of Q fever as a non occupational exposure.

Controlling and monitoring the transportation steroids of livestock via quarantine posts, following tick control strategies, equipping and completing a national diagnostic laboratory, drawing up a health agreement with neighbouring countries and the use of vaccines for domestic animals and high risk groups, can all be effective in preventing and controlling the

Fig. 1: The geographical distribution of samples tested for Q fever in Iran including the time of report, In all the symbols, white figures indicate negative and black figures show positive Q fever

disease (Angelakis and Raoult, 2010). The widespread application of such a vaccine in cattle in Slovakia in the 1970s and 1980s significantly reduced the occurrence of Q fever in that country (Kovacova and Kazar, 2002).

It should be emphasised that evidence of Q fever infection during the last 60 years in different regions of Iran and only few reports of the disease in our neighbouring countries and in the region, is mostly due to the fact that more surveys have been carried out in Iran, rather than anything exceptional happening in Iran. In fact recent studies recently carried out in countries such as Oman, Iraq, Afghanistan, United Arab Emirates, Turkey and Saudi Arabia have also shown the presence of the disease (Scrimgeour *et al*., 2003; Leung-Shea and Danaher, 2006; Lloyd *et al*., 2010; Bailey *et al*., 2011; Karabay *et al*., 2011; Hussein *et al*., 2012).

Based on these findings, it is recommended that a follow up study is designed to find acute or chronic human cases in high risk regions of the country. Following up infectious endocarditis cases may be a useful route to find the chronic cases. It is also recommended to do further prevalence studies on Coxiella infection among these high risk groups and the results be compared with the general population to elucidate the epidemiology of Q fever in Iran.

As with all zoonotic diseases, control of the disease in animals will influence the prevalence of the disease seen in humans. Therefore, close cooperation between veterinary organizations, the

Ministry of health and the Ministry of education, is necessary to promote the prevention and control programs for the disease in Iran. Since Q fever in humans is often an occupational hazard, vaccination should be considered primarily for exposed populations (Maurin and Raoult, 1999).

CONCLUSION

The purpose of the current study was to highlight the importance of Q fever as an emerging public health concern in Iran. This study showed that Q fever is a nationwide disease which is reported both in human and animals during the last 60 years in Iran. Based on the findings of this study, it would seem that Q fever disease has been neglected by the physicians and the national health system. Further interventions are strongly recommended to increase the Q fever case finding among the suspected human cases in Iran.

ACKNOWLEDGMENTS

This study was financially supported by Pasteur Institute of Iran (IPI) (Grant No. 582) and the authors would like to thank the research committee of IPI and Iran Center for Disease Control in Ministry of Health for awarding this grant.

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