



Q Fever in Individuals in the Eurasian Continent: A 50-Year Literature Review (1973 - 2022)

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Abstract

Q fever is a naturally occurring zoonotic disease with a zoonotic range covering all continents of the globe. The reservoirs and vectors of *Coxiella burnetii* are ixodid ticks and their hosts. This disease is characterized by a variety of mechanisms and routes in humans and animals (e.g., vector-borne, foodborne, airborne, and dust-borne). The disease often runs in the form of a fever. This article will review the incidence of human Q fever on the Eurasian continent over the past 50 years. Because Q fever is one of the unobserved infectious diseases, the occurrence of Q fever in humans in most countries is impossible to evaluate. Since this literature review is the primary resource for tracking scientific trends and research findings on the subject, the main goal of this study has focused on estimating the index of the incidence of Q fever infection among humans and compiling a 50-year literature review from August 1973 to July 2022. This study investigated the articles published in PubMed, Scopus, CyberLink, Web of Science, and Google Scholar by reviewing the scientific literature and official systematic reviews. The data were obtained using the keywords "Q fever AND prevalence/incidence" and "Q fever AND epidemiology." The incidence of Q fever varies considerably from country to country due to epidemiological differences and whether the disease is detectable or not. Depending on the location of the country, endemics or outbreaks occur. At the Third World Health Forum in 1950, the possible danger of Q fever to human health was realized, and decisions were made stimulating research into the global prevalence of the causative agent of the disease. Since then, numerous epidemiological studies have shown that Q fever occurs almost everywhere worldwide except in Antarctica and New Zealand. This review's available literature and ongoing epidemiological investigations in many countries show that Q fever needs to be regarded as a global community health issue. However, in the case of Kazakhstan, there is currently no information on the incidence of infection in humans and farm animals that requires further research on the incidence of Q fever, especially in coronavirus disease 2019.

Keywords: Q Fever, Epidemiology, *Coxiella burnetii*, Eurasian Continent, Incidence

1. Context

Q fever was first identified in Montana, the United States, and Queensland, Australia, and reported in the 1930s (1). The first descriptions of Q fever in humans were given in 1937 by Burnett, who surveyed multiple incidences of Australian slaughterhouse laborers who suffered from indistinguishable fever (2, 3). Within 1941 - 1944, during World War II, this disease was registered in German troops posted in the Balkans, southern Italy, Corsica, and British and American allied forces in central

Italy and the troops in Crimean and Ukrainian territories. Therefore, there are numerous terminologies for the infection, according to the location and extent of the disease, namely Euboea fever, Olympus fever, influenza, Crimean fever, Cretan pneumonia, Balkan influenza, 7-day fever, or Derrick-Burnett illness (4). The causative agent of the disease, formerly called *Rickettsia diaspora*, was initially identified in the United States by Cox and finally renamed *Coxiella burnetii* (5).

Q fever was prevalent everywhere where studies were conducted, except in New Zealand. The leading carriers

and accumulators of this disease are domestic animals. However, in the last few years, there has been an increase in the quantity of these species excreting the bacterium, including domestic mammals, marine mammals, reptiles, ticks, and birds (6). The route of transmission is mainly the inhalation of contaminated aerosols. However, the ingestion of infected raw milk can cause seroconversion. Person-to-person transmission can occur through the transfusions of infected blood, sexual contact, and contact with infected products of women giving birth. In humans, the disease is reported among individuals in close contact with infected animals and their products (7).

Q fever diagnosis is based on a set of clinical, epidemiological, and laboratory data (e.g., enzyme-linked immunosorbent assay, polymerase chain reaction, and bacteriological analysis), intradermal and biological samples, and chest X-ray. The incidence of Q fever in humans and animals cannot be assessed in most countries and remains unrecognized. Moreover, there is no epidemiologic surveillance for the disease. In addition, the symptoms of Q fever are nonspecific. Therefore, this illness needs further attention as a general public health issue in numerous countries.

In Kazakhstan, Q fever has not been monitored since the 1980s, and there is no epidemiological surveillance. Meanwhile, since 1995, there has been an increase in the number of cases of fevers of unspecified etiology among the residents of the southern region of Kazakhstan, with most cases being diagnosed based on clinical and epidemiological data without laboratory confirmation. In this group, Q fever might be present in a significant proportion as an etiological diagnosis. At the same time, a considerable number of brucellosis cases have been reported in the region. Given that the two infections' clinical presentations and epidemiological factors are often indistinguishable, Q fever might also be present in this group (8).

Q fever has a wide range of clinical manifestations, is often nonspecific, can last from a few days to more than a year, and is often misdiagnosed, thereby causing inadequate therapy. Furthermore, prolonged illness can lead to severe debilitating disease, and a person might become disabled. In addition, patients might experience more severe conditions in various organ systems. Q fever causes enormous economic damage to society by affecting livestock products and threatens humans' physical and mental health. Therefore, the present study aimed to evaluate the frequency of occurrence of this infectious disease among populations, based on published materials from August 1973 to July 2022, by reviewing the scientific literature and official systematic reviews.

2. Method

2.1. Search Strategy

This literature review of English- and Russian-language publications was conducted regarding the prevalence of Q fever. The current review analyzed the literature sources from some databases, including PubMed, Scopus, Web of Science, Google Scholar, and CyberLink.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria to conduct the literature review of the prevalence of Q fever were the articles that reported or had data on the majority of Q fever cases, the papers published between 1973 - 2022, and full-text articles, original studies, randomized trials, meta-analyses, reviews, and systematic reviews published in scientific journals. The articles were excluded if they did not report on Q fever prevalence and were unrelated to humans. Moreover, the unreviewed sources or other scientific works (i.e., abstracts, posters, books, papers, clinical trials, and reports) not published in scientific journals were excluded from the review.

Some keywords were identified for the review, namely "Q fever AND prevalence/incidence" and "Q fever AND epidemiology." The period of the literature search was 1973 - 2022. The total number of studies analyzed in this literature review was 54 publications.

3. Results and Discussion

3.1. Prevalence of Q Fever in the European Continent

On the European continent, in the early 1940s, over 1000 cases of these infectious diseases were confirmed infections of servicemen from the Balkan region. During recent decades, massive flares have been recorded. Additionally, serological surveys have shown a seroprevalence of 2-14% in populations (5, 9). Up to 2007, Q fever was rare in Europe, according to the European Center for Disease Prevention and Control (ECDC). In Europe, the ECDC carries out regular epidemiological surveillance; therefore, according to monitoring data, only 1023 out of 4245 cases of Q fever confirmed in 2013 - 2017 were registered by European countries (10).

In Germany, the rate rose to 0.8 in a million individuals between 1979 - 1989 and 1.4 in a million of the general public between 1990 - 1999. In addition, this disease is endemic, with 27 - 100 cases of Q fever per year, and 40 outbreaks of Q fever have been reported (11, 12). In May 1996, an illness with Q fever erupted in Rollshausen, Germany, and one-half of the surrounding Lore region cities (12, 13). A retrospective cohort study was performed on

residents of Rollshausen over the age of 15. The sera from 200 residents were tested by enzyme immunoassay for antibodies resistant to the causative agent of the disease. The results of clinical and serological studies indicated that 45 (23%) of the 200 inhabitants were observed to be infected with *C. burnetii*. The incidence was equal in males and females and various age groups. In 2005, there was a significant outbreak of Q fever in Germany caused by sheep breeding near residential areas (14).

In the United Kingdom, between 1975 - 1995, the laboratories in England and Wales reported 67 to 169 cases of Q fever annually to the Communicable Disease Surveillance Center. This represented a constant occurrence of 15 - 35 cases per every 100000 of total patients' number on an annual basis. The most frequent cases of Q fever among the 641 cases detected between 1991 - 1995 in England, Wales, Northern Ireland, and the Channel Islands were mainly older males (15). Within 1980 - 1996, eight outbreaks were identified around the United Kingdom, including general population (16), 14 cases in southwest England in the same report in laboratory employees after contact with experimentally infected sheep (17), a 25-case study of postal workers in Oxford in 1983 (18), 2 laboratory incidents in Northern Ireland during 1986 (19), and 5 cases among schoolchildren allegedly infected by livestock, including domestic birds and goats, in southwest England in 1987 (20). There were 147 issues in the Midlands and 47 patients across Northern Ireland during 1989 (19, 21) and four issues in the Isle of Wight in 1992 among the members of the recycling workforce (22).

In the Netherlands, from 1975 to 2006, the yearly number of cases increased from 0 to 32 per annum. However, between 2007 - 2009, the number of cases rose to over 2300 in 2009, the highest number ever reported (23). Before 2007, 5 - 16 cases of Q fever were reported annually in the Netherlands (24, 25). The Netherlands experienced the largest outbreak of Q fever on record from 2007 - 2010; over 4000 cases were reported, and the estimated number exceeded 40000 (26, 27). The province of North Brabant was the region with the highest infection rate (28).

Switzerland had a significant outbreak with 415 cases of Q fever in 1983 (29). During an episode of Q fever in the Spanish Canary Islands, 36% seroprevalence of infection among humans was recorded (30). In Spain, the relevance of Q fever differs significantly among considered regions. For example, although major outbreaks have been recorded in the Basque region, only a few cases have been notified from other regions (31). The National Center for Microbiology, Virology and Immunology, Sanitaria, between 1981 - 1985, serologically diagnosed 249 episodes of Q fever from different regions of Spain. Most incidents

were random; however, the instances from two flare-ups (i.e., a total of 51 occurrences) were entered into the trial. They comprised an estimated 234 and 15 reports of an acute and chronic Q fever, respectively, correspondingly (6%), with 14 reports of infected patients diagnosed with cardiac endocarditis. The highest incidence of severe cases was in admitted patients with atypical pneumonia (75%) or high fever (18%). The involvement of the liver was observed in 7.4% and 19% of patients with pneumonia or febrile illness, respectively. Most cases (77.1%) were males aged 15 - 44 years, presumably reflecting occupational risks (32).

Spanish records show more than 600 occurrences of Q fever, the majority of which occurred sporadically, excluding three flare-ups during 1989 (5 occurrences), 1990 (30 occurrences), and 1998 (14 occurrences) (26, 27). From 2000 - 2009, 100 cases of Q fever were recorded, the highest epidemic, with an outbreak in Asturias (60 incidents in 2003) and two occasions in Madrid. Most incidents occurred during 2015 (26 incidents) and 2014 (11 incidents). It is worth noting that they were all reported between December - June (i.e., in the winter and spring) (28). The illness seemed less familiar in the central and southern regions of the country (32). Interestingly, the main clinical manifestations of Q fever vary from one region of Spain to another. Q fever in pneumonia is best known around the Basque region of Northern Spain (32, 33); however, hepatitis is predominant in Southern Spain (34).

Q Fever is highly endemic in an area of Basque (33, 35). In various parts of France, cases of Q fever are reported to occur sporadically; the illness was tested mainly in the south of the country, near Marseille. However, this issue represents the impact of the National Reference Stations for rickettsioses there rather than the higher frequency of the illness. In a seroprevalence study conducted by Tissot Dupont et al. in 1992, in 942 donor serum samples in Marseille, specific antibodies to *C. burnetii* were detected in 38 samples (36). The highest prevalence reported in France was in rural populations in the Alps, where specific antibodies were detected in 30% of the rural population (37).

Large outbreaks in Italy with Q fever occurred in the summer and autumn in northeastern Italy (38). A 33-veterinarian team became infected with Q fever while attending a medical practice in Slovenia in 2007 (39). A total of 155 Q fever patients were hospitalized in Split, Croatia, between 1985 - 2002 (40). In 2000, an outbreak of Q fever was reported in Albania in a group of 115 police officers from Argentina who had been exposed to contaminated dust from infected sheep in Prizren in southern Kosovo, including 42 cases with clinical symptoms of Q fever (41).

More than 20 Q fever outbreaks occurred in Bulgaria between 1949 - 1993 (42). At the end of 2010, there were 139 confirmed incidences of Q fever (43). Before 1993, the prevalence of infection in Slovakia was reported as 3% (44). According to the International Epizootic Bureau, between 1996 - 2001, there were 8 cases of Q fever in Hungary, 26 cases in Kyiv, Ukraine, and 138 cases in Yugoslavia. In Bulgaria, Q fever is a notifiable disease, and the European Union case definition and classification of cases are used for surveillance purposes. In Bulgaria, the incidence of Q fever remained low from 2011 - 2017, with mostly sporadic cases and two small outbreaks (45).

In Greece, Q fever emerged in 1946, probably due to eating milk from infected sheep (46). In 2009, there were 58 cases of Q fever (47). In Turkey, Q fever is considered endemic. Before 1953, 191 occurrences of Q fever were documented, the majority of which were incidental (48). In 2002, 46 cases were registered in the Black Sea region of Northern Turkey, 19 cases of which were reported with verified severe Q fever.

According to official Russian data, between 1957 - 1995, there were 11058 cases in 37 regional areas, consisting of 39% in the Volga region, 31% in Western Siberia, and 14% in the Chernozem region, mainly in the regions of Astrakhan, Novosibirsk, and Voronezh. Cases of Q fever from goats and sheep reservoirs have been reported in recent years, mainly in the European and Asian parts of Russia, including the outbreaks in the Novosibirsk and Voronezh regions and the Altai region (5). Sporadic morbidity has been reported in the Russian Federation, with annual fluctuations ranging from 225 (in 1993) to 31 (in 2014) cases (49). In 2018, according to the Federal Center for Hygiene and Epidemiology, 110 cases of Q fever were registered. Throughout the study years, the incidence rate ranged from 1.0 per 100000 individuals in 1957 to 0.02 in 2014.

3.2. Prevalence of Q Fever in the Asian Continent

The first clinical cases of acute Q fever were registered in Iran in 1952. From 1970 - 1976, 133 patients with acute Q fever were registered from various regions of Iran (50). In Iran, this infection is not given the attention it deserves since 1976, and there have not been any instances of human illness. However, at the same time as the major eruption of this infectious disease in the Netherlands (2007 - 2010), the causative agent of the disease was detected in hectic residents in Kerman, and investigation for this disease restarted. The geographic distribution of seropositivity of *C. burnetii* Q fever was observed in individuals from nine provinces. The largest areas of distribution of immunoglobulin G antibodies of phases I

and II were observed in the provinces of Kerman (24%) and South Khorasan (54%) (51).

The disease was first reported in China in 1950. Over the past 25 years (1989 - 2013), 29 reports of Q fever have been published in China, almost half of which were reported in the past 5 years. These publications were mainly in China, and the current review summarized the findings to better understand Q fever in China. The overall prevalence of *C. burnetii* infections reported is 10% (1139/11209) in humans. These infections are widespread in China. Accordingly, positive humans and/or animals were reported in 64 cities/municipalities from 19 provinces, especially in the eastern, western, and northern regions (52).

An episode of Q fever resulted in 22 (58%) of the 38 marines deployed to Iraq in 2005. The frequent occurrences were fever (in 100% of patients), respiratory signs (76%), and digestive signs (53%). Potential risk factors were dust and contact with animals and ticks (53). The number of Q fever cases has increased rapidly in South Korea since 2015 (54).

4. Conclusions

The incidence of Q fever varies significantly from nation to nation due to epidemiological differences and whether the disease is reportable. Depending on the location of the country, endemic or outbreak situations occur. In endemic areas, Q fever appears as an incidental occurrence, typically following defined perilous actions (e.g., slaughterhouse jobs and agriculture). In the third world healthcare forum in 1950, the possible risk of Q fever to individuals' health was realized, and decisions were made encouraging the investigation of the global incidence of the causative agent of this disease. Since then, numerous epidemiological surveys revealed that Q fever occurs nearly worldwide, except in Antarctica and New Zealand.

Given that the data on the prevalence of seropositive disease are available for many nationalities, it is reasonable to assume at this point that the actual prevalence of human Q fever has been mostly undervalued. Because Q fever is a precipitated contagious infection, symptomless variants are predominant. Q fever is seldom a reportable infection; therefore, required reporting does not exist, and the few local reports written in languages other than English continue to be ignored. Since Q fever is rarely a mandatorily reportable disease, it is impossible to estimate its incidence in most countries. However, the available literature in this review and current surveillance surveys indicate that Q fever must be regarded as a significant public health issue in several countries, including France, Great Britain, Germany, Spain, and

Italy, as too many lands in which Q fever would be expected although not recognized due to the inadequate surveillance of the disease. Q fever continues to be mainly a work-related risk for individuals who have contact with domestic animals.

Footnotes

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