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Q Fever: A Re-Emerging Disease?

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Abstract

Q fever is a mainly airborne zoonosis with public health concern throughout the world caused by the highly contagious, obligate intracellular bacteria *Coxiella burnetii*. It is an important occupational zoonosis since its discovery in 1935; it has been shown to infect a wide range of hosts, including humans. Although Q fever is a disease closely related to occupations such as handling livestock, most of the previous studies concerned with general population. A recent outbreak in Europe reminds us that this is still a significant pathogen of concern, very transmissible with a very low infectious dose. For these reasons it has also featured regularly on various threat lists, as it may be considered to be used as a bio-weapon. Therefore, we reviewed the literatures on Q fever to highlight the epidemiologic, economic and public health impact of Q fever as a basis for designing effective control strategies.

Keywords: Q fever; Epidemiology; Public health hazards

Introduction

Q fever is an important occupational zoonotic disease caused by the obligate intracellular bacterium *Coxiella burnetii* and has great public health significance worldwide [1]. The disease first described in 1937 in Queensland by E.H. Derrick in association with the meat and livestock industry [2]. Q fever is a mainly airborne zoonosis, infection in domestic animals is usually chronic and dormant; the infected pregnant animals excrete the organism into the environment in birth fluids, placenta, fetal membranes, urine and faeces [3].The most commonly identified sources of human infection are farm animals, especially cattle, goats and sheep, which constitute the best known reservoirs of *C.burnetii* [3]. Based on epidemiological evidences, the main route of infection in humans is inhalation of contaminated aerosol or dust containing bacteria shed by infected animals. Oral transmission is also discussed and the consumption of contaminated raw milk and dairy-products represents a potential source of human infection [4,5]. The epidemiology and the exact modes of transmission of Q fever remains to be elucidated. Therefore, further research is necessary to improve knowledge of the disease itself. We reviewed the literatures to highlight the epidemiologic, economic and public health impact of Q fever as a basis for designing effective control strategies.

History

The term "Q fever" (for query fever) was proposed in 1937 by Edward Holbrook Derrick to describe febrile illnesses in abattoir workers in Brisbane, Queensland, Australia. In 1935, a disease of unknown origin was first observed in slaughterhouse workers. Patients presented with fever, headache, and malaise. Serologic tests for a wide variety of possible etiologic agents were negative [2]. Because the disease had an unknown aetiology, it was given the name Q fever (for query). The etiologic agent was thought to be a virus [6]. Subsequently, Berri et al. isolated a fastidious intracellular bacterium from guinea pigs that had been injected with blood or urine from Derrick's patients and named it *Rickettsia burnetii* [3]. This bacterium was morphologically and biochemically similar to other gram-negative bacteria. On the basis of cultural and biochemical characteristics, Philip classified *Rickettsia burnetii* in a new genus [7], Coxiella, named after Herald R. Cox, who first isolated this microorganism in the United States from ticks, Dermacentor andersoni, and named it *Rickettsia diapora*. The two organisms were subsequently shown to be identical and are now known as *C. burnetii*, since then, it has been isolated from several mammals and from ticks, and it may persist in the environment.

Etiological Agent

Q fever results from infection by *C. burnetii*. This organism is an obligate intracellular pathogen, it can be grown only in embryonated eggs or cell cultures or, when necessary, in inoculated laboratory animals. It is a small pleomorphic rod (0.2–0.4 mm wide, 0.4–1.0 mm long) with a membrane similar to that of a Gram-negative bacterium [8]. It has been traditionally placed in the family Rickettsiaceae; however, recent phylogenetic studies have demonstrated that *C. burnetii* is more closely related to *Legionella*, *Francisella* and *Rickettsiella*. This organism is now classified in the family Coxiellaceae and order Legionellales in the gamma subdivision of Proteobacteria [9]. Unlike rickettsiae, *C. burnetii* produces a small, dense, highly resistant spore-like form that is highly stable in the environment [10]. This ability has been attributed to the existence of *C. burnetii* developmental cycle variants: large-cell variants (LCV), small-cell variants (SCV), and small dense cells (SDC) [11]. The SDC and SCV represent the forms of the bacteria likely to survive extracellularly as infectious particles, as well as its capability to survive relatively extreme environmental conditions. The SCV is resistant to heat, pressure, and chemical agents [12]. The large cell variants (LCVs) are probably the metabolically active cells of this organism. It undergoes sporogenic differentiation to produce resistant, spore-like forms, the small-cell variants. These are released when the cells lyse and can survive for long periods in the environment [13]. This organism also has two distinct antigenic phases, phase I and phase II. Phase I and II cells are morphologically identical, but differ in some biochemical characteristics including their lipopolysaccharide (LPS) composition. Organisms isolated from infected animals or humans express phase I antigens and are highly infectious. Organisms expressing phase II antigens are less infectious and are recovered after the bacteria are passaged repeatedly in cell cultures or eggs. Experimentally infected animals first produce antibodies to phase II antigens and later produce antibodies to phase I antigens. A similar response occurs in humans,

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and is used to distinguish acute from chronic infection [14]. It has the capability to survive permanently inside the macrophages, causing a chronic disease after an acute episode.

Epidemiology

Q fever has been described worldwide. Two characteristics of the organism are important in the epidemiology of the disease. These are its ability to withstand harsh environmental conditions, probably as a result of spore formation [10], and its extraordinary virulence for man. A single organism can cause disease in man [15]. *C. burnetii* has been a very successful pathogen. By 1955, Q fever had been reported from 51 countries on five continents [16]. From 1999 to 2004, there were 18 reported outbreaks of Q fever from 12 different countries [17]. Q fever considered as a public health problem in many countries, including France, the United Kingdom, Italy, Spain, Germany, Israel, Greece, and Canada (Nova Scotia). In France the incidence of acute Q fever is estimated at 50 per 100,000 inhabitants per year, and that of Q fever endocarditis is estimated at 1 per 106 inhabitants per year [18]. From 1975 to 1995, 67 to 169 Q fever cases were reported annually in United Kingdom to the Communicable Disease Surveillance Center by laboratories in England and Wales [19]. This represents a stable incidence ranging from 0.15 to 0.35 cases per 100,000 population per year. Q fever is endemic in Israel between 1981 and 1990, 758 Q fever cases were reported to the Ministry of Health [20]. A series of 34 patients with Q fever endocarditis was reported more recently [21]. In Germany it is considered as a notifiable disease, 27 to 100 cases are reported annually [22]. In May 1996, a Q fever outbreak occurred in Rollshausen and five surrounding towns in the district of Lohra [22,23]. In this rural area, two flocks of sheep (1,000 to 2,000 and 20 animals, respectively) had been kept near Rollshausen before the Q fever outbreak. Lambing occurred in December 1995 and January 1996. 7.8% out of 21,191 tested cattle, 1.3% of 1346 tested sheep, and 2.5% of 278 tested goats had evidence of *C. burnetii* infection [24]. The largest previously described outbreak occurred in 2003, associated with a farmers' market in Soest [25]. Infected sheep have been implicated as the source of infection in 24 out of 40 documented outbreaks reported in Germany between 1947 and 1999 [24]. In Cyprus, the prevalence of IgG antibodies against *C. burnetii* phase II antigen was estimated at 48.2% for goats, 18.9% for sheep, and 24% for bovines [26]. In Iran, goats had a significantly higher average seroprevalence (65.78%) than cattle (10.75%) [27]. In Zimbabwe, serological evidence of Q fever infection was found in 39% of cattle, and in 10% of goats [28]. In the USA goats had a significantly higher average seroprevalence (41.6%) than sheep (16.5%) or cattle (3.4%) [29]. From 2007 to 2009, the Netherlands faced large seasonal outbreaks of Q fever, with the highest peak in 2009 [30]. Surveillance of Q fever is mandatory in European Union (EU) countries. In 2009, a total of 370 Q fever cases were reported in 24 EU countries, apart from the 2,317 cases from the 2009 outbreak in the Netherlands [31]. The low number of notifications is in contrast to results from seroprevalence studies, which suggest that 2–10% of the general population in EU countries, have previously been infected with *C. burnetii* [32].

A wide variety of animals can be infected with *C. burnetii*, including: domesticated animals such as cows, goats, sheep, dogs, and cats; non-human primates; wild rodents and small mammals; big game wildlife; and non-mammalian animals, including reptiles, amphibians, birds (domesticated and wild), fish, and many ticks. Over 40 ticks' species can be naturally infected [4]. They are likely to play a significant role in transmission among wild vertebrates, but are not considered to be essential in the cycle of *C. burnetii* infection in livestock [33]. However, the organism multiply in the gut cells of ticks and large numbers of *C. burnetii* are shed in tick feces [13]. Contaminated hides and wool may be a source of infection for people either by direct contact or after the faeces have dried and been inhaled as airborne dust particles. Heavy concentrations of microorganisms are secreted in milk, urine, feces, and especially in parturient products of infected pregnant animals. Because of the stability of this agent, dried, infectious particles in barnyards, pastures, and stalls can be a source of infection for periods of up to 150 days [34]. During chronic infection, *C. burnetii* is mainly found in the uterus and mammary glands [33]. Shedding of *C. burnetii* into the environment mainly occurs during parturition; over 10^9 bacteria are released at the time of delivery [33]. Goats and cows mostly shed *C. burnetii* in milk and vaginal mucus [35,36] whereas ovines shed mostly in faeces [35]. Goats and cows shed *C. burnetii* in milk for several months or years [37].

The aerosol route (inhalation of infected fomites) is the primary mode of human contamination with *C. burnetii* [38]. Ingestion (mainly drinking raw milk) is probably a minor factor in the transmission of *C. burnetii* [39] and is now a point of controversy concerning the possibility of infection by oral route [40]. Further research is required to clarify the probability of infection by oral route. If infection by oral route is proven to be efficient, the sufficient number of pathogens capable of causing Q fever should be determined [41].

Person-to-person transmission is extremely rare. Although infrequent, sporadic human Q fever cases have occurred following contact with an infected parturient woman (in an obstetrician who performed an abortion on the pregnant woman) [42]. The infection can also be spread by the wind [43]. Thus, Q fever may occur in patients without any evident contact with animals.

Q Fever in Animals

Coxiella burnetii can infect a large number of animal species including livestock [33]**.** Infections in animals are usually asymptomatic and are not considered a veterinary problem. When clinical disease occurs, reproductive failure is usually the only symptom presented. Reproductive failure can be manifested as abortions, stillbirths, retained placenta, infertility, weak newborns and mastitis in dairy cattle. Anorexia and abortions have been reported more frequently in sheep and goats, while infertility, sporadic abortion and low birth weights are seen in cattle [44]. *C. burnetii* localises in the uterus and mammary glands of infected animals [33,45]. Epidemiological data indicate that dairy cows are more frequently chronically infected than sheep and thus may represent the most important source of human infection.

Q Fever in Human

Humans are the only species to develop symptomatic disease. The spectrum of illness in man is wide and consists of acute and chronic forms. The infectious dose is estimated to be 10 microorganisms or fewer [46]. The infections are primarily found in persons occupationally exposed, such as ranchers, veterinarians, and workers in meatpacking plants. Domestic ungulates, such as cattle, sheep, and goats, usually acquire and transmit *C burnetii*; domestic pets (primarily cats) can be a primary source of human infection in urban environments [47,48]. The classic presentation is a flulike illness manifested by fevers, sweats, cough (productive at times), myalgias, and arthralgias. A high percentage of patients also have pneumonia and hepatitis. Pneumonia is typically mild, but progression to acute respiratory distress syndrome can occur [49]. Acute Q fever is found primarily as a granulomatous hepatitis. However, in patients infected by the aerosol route, Q fever pneumonia is more common. Life-threatening complications may

occur, including meningoencephalitis, myocarditis, or pericarditis. The infectious doses have been shown to vary inversely with the length of the incubation period [34]. Person-to-person transmission is very rare, although exposure during childbirth, through sexual transmission and blood transfusions, is possible [50].

Diagnosis

The isolation of the pathogen is the gold standard but it remains time consuming and hazardous and therefore restricted to specialized laboratories [51]. Conventional diagnosis of Q fever is mainly based on serological tests such as immunofluorescence, enzyme linked immunosorbent assay and complement fixation test. Immunofluorescence assay (IFA) is currently used as the 'Reference' method for the serodiagnosis of Q fever and it can differentiate antibodies to phase I and phase II variants in IgG, IgM and IgA fractions [52]. The enzyme-linked immunosorbent assay (ELISA) has been reported to be sensitive, easy to perform, with a potential for adoptability for automation, and can be applied in epidemiological survey. It has been shown to be of value for the diagnosis of acute and chronic Q fever [53]. Currently, the polymerase chain reaction (PCR) is one of the most analytically sensitive and rapid means for both the direct detection of *C. burnetii* and the identification of shedders. PCR can be used on a wide range of samples (vaginal discharge, abortion material, faeces and milk (bulk or individual)). It has become increasingly common in diagnostic laboratories with PCR capability [54,55]. The level of detection of conventional PCR is related to the sample under investigation (1–500 bacteria/ml of milk; 1 bacteria/mg of faeces). Several target genes have been used, such as the multicopy insertion sequence (IS1111) or single copy genes encoding various proteins (e.g dismutase [sodB]; com1 encoding a 27 kDa outer membrane protein; heat shock proteins [htpA and htpB]; isocitrate dehydrogenase [icd]; macrophage infectivity potentiator protein [cbmip]). Real-time PCR techniques have also been described [56,57]. For routine diagnostics, it is widely accepted that real-time PCR technology is preferable to conventional gel-based detection methods. It allows high sample throughput, has a reduced potential for carry-over contamination and is best suited for quantification of *C. burnetii* in biological samples. Several typing methods have been used for the characterization of *C. burnetii* strains, including restriction endonucleae of genomic DNA [58], PFGE (pulsed-field gel electrophoresis) [59,60], and sequence and/or PCR-RFLP (restriction fragment length polymorphism) analysis of icd, com1 and mucZ genes. More recently, two PCR-based typing methods have been described, MLVA (multi-locus variable number of tandem repeats analysis) [5,61] and multispacer sequence typing (MST) [62]. These methods may become very useful for epidemiological investigations.

Multilocus Variable-number tandem-repeat Analyses (MLVA) is based on variation in repeat number in tandemly repeated DNA elements on multiple loci in the genome of *C. burnetii* and might be more discriminatory than multispacer sequence typing [63]. MLVA also can be performed on *C. burnetii* strains [5] or directly on DNA extracted from clinical samples [64]. A total of 17 different minisatellite and microsatellite repeat markers have been described [5].

Prevention and Control

In case of Q fever outbreak, sanitary and prophylactic measures should be applied at herd and human level, in order to limit disease transmission. Human-to-human transmission is extremely rare and Q fever is mainly an airborne disease, measures of prevention are aimed at avoiding the exposure of humans and particularly persons at risk, to animal and environmental contamination. To prevent and reduce the animal and environmental contamination, several actions can be proposed. *C. burnetii* can be reduced in the farm environment by regular cleaning and disinfection of animal facilities, with particular care of parturition areas, using 10% sodium hypochlorite. In the UK, Health Protection Agency guidelines suggest the use of 2% formaldehyde, 1% Lysol, 5% hydrogen peroxide, 70% ethanol, or 5% chloroform for decontamination of surfaces [65]. Pregnant animals must be kept in separate pens, placentas and aborted fetuses must be removed quickly and disposed under hygienic condition to avoid being ingested by dogs, cats or wildlife. Spreading manure from contaminated farms in suburban areas and gardens should be avoided. In order to acquire and maintain *Coxiella*-free livestock, introduction of animals, regrouping of flocks, contacts with wildlife and infestation by ticks should be minimized. These methods may be effective in controlling disease but exposed animals may remain infected. Although vaccines for animal Q fever have been developed, there are not commercially available in most countries [32,66]. At human level, prevention of exposure to animals or wearing gloves and masks during manipulation of animals or their litter is advised [67].

Since Q fever is enzootic among wild and domestic animals, controlling *C. burnetii* infection in susceptible animals is difficult. The only way to really prevent the disease in ruminants is to vaccinate uninfected flocks, with an efficient vaccine. Vaccines can prevent abortion in animals, and it is evident that a phase I vaccine must be used to control the disease and to reduce environmental contamination and thus, the risk of transmission to humans. The widespread application of such vaccine in cattle in Slovakia in the 1970s and 1980s significantly reduced the occurrence of Q fever in that country [68].

Finally, it is important to remember that *C. burnetii* is extremely hazardous to humans, and laboratory infections are common. Because of its ability to cause incapacitating disease in large groups of people, its low infectious dose, resistance in the environment, and aerosol route of transmission, *C. burnetii* is considered a potential agent of bioterrorism and is classified by the CDC as a group B agent. Appropriate precautions must be taken with these risk group 3 agents. Live culture or contaminated material from infected animals must only be handled in facilities that meet the requirements for containment group 3 pathogens.

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