Q fever

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Q fever is a zoonotic disease first identified in Queensland, Australia, in 1935, after an outbreak of febrile illness among slaughterhouse workers.[1] The disease was named "**Query (Q)**" fever, because its etiopathogenesis was not known. In 1935, researchers in the United States isolated a rickettsial agent from ticks that they called Nine Mile agent, which was subsequently linked to a laboratory-acquired human infection.[2,3] The agents were later determined to be identical and were eventually named *Coxiella burnetii* in honor of Harold Cox and MacFarlane Burnet, 2 prominent early researchers.

Since its discovery, Q fever has been reported worldwide with the exception of New Zealand.[4] *Coxiella burnetii* is most commonly transmitted to humans by direct contact with the reproductive tissues of cattle, sheep, and goats in which the causative organism reaches exceptionally high titers. Disease outbreaks have been associated with slaughterhouses, farms, and institutions with intensive sheep research programs.[5] Sporadic human infections have also been linked to parturient domestic animals, such as dogs and cats.[6] Aerosol transmission of *C burnetii* occurs through the inhalation of contaminated materials,[7] and large human outbreaks have been linked to wind dispersion from sites where infected animals are kept.[8-9]

Pathogen Characteristics

Coxiella burnetii is a gram-negative coccobacillus that resides and replicates in host monocytes and macrophages.[10] The agent has 2 distinct life cycle stages known as the **large-cell variant (LCV)**, which is the vegetative form of the bacteria seen in infected cells, and the **small-cell variant (SCV)**. The SCV may be metabolically inactive and is the extracellular and presumably infectious form of the organism.[10,11] The SCV form of *C burnetii* is likely to be long-lived in the environment because of its resistance to osmotic stress and physical disruption, as well as its hardy resistance to chemical and physical agents.[10,12-14]

Coxiella burnetii undergoes phase variation of outer cell surface antigens, which is of relevance to the serologic diagnosis of Q fever. Sequential passage of *C burnetii* through immune incompetent hosts, such as embryonated eggs, leads to the development of avirulent organisms with markedly different antigenic profiles than fully virulent organisms.[15,16] Although virulent organisms display predominantly phase I outer surface antigens composed of lipopolysaccharide O antigens, avirulent organisms display mainly phase II protein antigens.[17] Differential antibody responses to phase I and phase II antigens are useful for distinguishing acute from chronic Q fever in humans (as discussed under "Diagnosis").

In the host, *C burnetii* has an affinity for placenta, and concentrations as high as 10^9 ID_{50} (the infectious dose sufficient to infect 50% of those exposed) have been reported per gram of placental tissue.[7] The *C burnetii* SCV is shed in birthing fluids and membranes,[7] as well as milk, urine, and feces, and infection is typically acquired through the inhalation of the organism in fine-particle aerosols. Contact with droplets or fomites may also result in transmission. Ingestion has been proposed as a route of transmission, particularly through the consumption of contaminated, unpasteurized dairy products.[18] However, this mode of transmission is difficult to demonstrate and probably does not play an important role in the spread of disease to humans.[10,19] Sexual transmission of *C burnetii* among humans has been documented, although this route is thought to be uncommon.[20] Although direct exposure to parturient animals or their birthing products poses the highest risk for Q fever, the organism's ability to persist in the environment may result in a continued risk for infection weeks to months after the birthing event. The potential for transmission is greatly enhanced by the extremely low infectious dose for *C burnetii*, which is reported to be as small as a single organism.[21]

Q Fever in Humans

Among humans, the spectrum of severity of Q fever is broad. The incubation period ranges from 1 to 3 weeks after exposure. As many as 50% of exposed persons may develop an antibody response without having signs of clinical illness. The acute disease is generally nonspecific and may include fever (75 to 91%), headache (53 to 67%), myalgias (38 to 73%), and cough (approximately 38%)[22-25]; other common symptoms may include fatigue, rigors, night sweats, and nausea or vomiting. In France, 34% of patients with acute Q fever have clinical signs of pulmonary disease, and 27% have abnormal findings on thoracic

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radiography.[22] Over 60% of patients may have high liver enzyme activities, and granulomatous hepatitis has been reported in as many as 40%.[22] In Australia, a chronic fatigue-like illness has been reported in as many as 10% of patients immediately following acute Q fever.[26] Meningoencephalitis and myocarditis are potential rare complications of acute Q fever.[22] Most patients with acute Q fever recover without medical intervention; however, treatment with doxycycline may shorten the clinical course of illness.[27]

Approximately 1 to 2% of patients acutely infected with *C burnetii* go on to develop chronic infection, although sequelae may not be manifested for decades after acute infection.[10,28] Because some acutely infected individuals may be asymptomatic or have only mild illness, development of chronic disease may be the first time Q fever is recognized. One of the most common sequelae of chronic Q fever is endocarditis.[22,29] Chronic granulomatous hepatitis, osteoarticular infection, pericarditis, and vascular complications have also been reported.[22,30,31] Persons with underlying heart valve abnormalities, prosthetic valves, or immune compromise are at increased risk for Q fever endocarditis. Chronic Q fever endocarditis can be life threatening, and patients may require excision and replacement of affected valves. Treatment consists of long-term administration of doxycycline and hydroxychloroquine.[32]

Q Fever in Animals

Animals typically acquire Q fever through exposure to other infected animals, either through direct contact with contaminated body fluids or aerosol exposure to infectious materials. Sheep, cattle, and goats are considered the most common livestock reservoirs for *C burnetii* on the basis of epidemiologic and laboratory evidence. Cats and dogs are also susceptible to infection and may transmit *C burnetii* to humans.[6,33,34] Antibodies against *C burnetii* have been detected among many wildlife species, including snowshoe hares, moose, and white-tailed deer in Nova Scotia; wild Dall sheep in Alaska; and black bears in Idaho and California.[35-37] Q fever among humans has been reported after contact with wild rabbits.[38] Rodents are susceptible to *C burnetii* infection and may play a role in the natural maintenance of Q fever among wildlife.[39]

Coxiella burnetii has been isolated from a wide variety of tick species and may be transmitted among animals via tick bite. The original prototype strain of *C burnetii* was isolated from a *Dermacentor andersoni* tick collected from Nine Mile Creek in Montana.[2] Ticks are not thought to play an important role in transmission of *C burnetii* to humans, but may be essential in natural maintenance cycles.

In ruminants, Q fever occasionally results in abortion, stillbirths, and complicated deliveries. Experimentally infected sheep are pyrectic, anorectic, and tachypneic, followed by delivery of stillborn or unviable lambs[40]; aborted fetuses may appear thin but grossly normal. However, animals with naturally acquired *C burnetii* infections frequently have no signs of illness and deliver normally while serving as a source of infection to humans and other animals. In herds with large numbers of naïve animals, Q fever has caused abortion storms in which a high percentage of animals have abortions.[41-43]

Little information is available on the effectiveness of treating Q fever in animals with antimicrobials. Tetracycline (8 mg/kg [3.6 mg/lb], PO) may be administered in water for several weeks prior to expected dates of parturition in ruminant herds in which Q fever is enzootic.[44] This prophylactic treatment is used to minimize shedding of the organism in the placenta and birthing fluids rather than to eliminate infection, and its efficacy has not been well evaluated.

Diagnosis

Because the clinical signs of Q fever are nonspecific, laboratory evidence of infection is needed for diagnosis. Four categories of diagnostic tests are available: isolation of the organism, which must be conducted in a biosafety-level 3 laboratory using tissue-culture; laboratory animals, or embryonated eggs; serologic tests, including **indirect fluorescent antibody (IFA)**, enzyme immunoassay, and complement fixation; antigen detection assays, including **immunohistochemical staining (IHC)**; and nucleic acid detection assays, including **polymerase chain reaction (PCR)** assays.

In humans, acute Q fever is most commonly diagnosed by use of IFA. Because antibodies against Q fever may develop late in the clinical course of disease, paired serum specimens should be tested; evidence of IgG antibody seroconversion or the presence of IgM antibody indicates recent acute infection. During acute infection, the body produces higher antibody concentrations to *C burnetii* phase II antigen. Titers are highest to phase I antigen in chronic infections, and the IgG phase II:I antibody ratio is widely used to distinguish acute from chronic infection. Culture, IHC, and PCR can be used to detect *C burnetii* in heart valve tissue from patients with endocarditis. Culture and PCR have also been used to diagnose acute or chronic Q fever by using whole blood samples; however, the diagnostic sensitivity of these techniques is lowered by prior antimicrobial administration.

Serologic diagnosis of Q fever in animals can be difficult. Phase I and phase II antibody responses have not been well evaluated in domestic animals, and IgG-based antibody tests provide only evidence of past exposure. Serologic tests are not useful for determining which animals represent a current risk for transmission, as animals may seroconvert without shedding or remain seropositive long after the acute infection has resolved. Conversely, some animals may shed *C burnetii* and pose a risk for infection prior to the development of antibodies, and some infected animals never seroconvert.[45,46] Detection of *C burnetii* antibodies in pooled milk has been used to assess infection within herds. Culture, IHC, and PCR assay may be used to diagnose Q fever by using placental tissue. *Coxiella burnetii* infection in placental tissue typically appears as a necrotizing placentitis with trophoblasts filled with small coccobacilli, and placental tissue may be considerably inflamed and necrotic.[47] In contrast, aborted fetal tissue rarely has any pathologic changes.

Q Fever in the United States

It is difficult to describe the epidemologic characteristics of Q fever in the United States, because it is not a notifiable disease in many states. Furthermore, the disease is generally underrecognized because of the nonspecific nature of clinical signs and the need for laboratory confirmation. Limited national surveillance data for Q fever in humans in the United States are available for the years 1948 through 1986; during this time, less than 30 states required reporting of Q fever. Between 1948 and 1977, a total of 1,168 cases of Q fever were reported to the Centers for Disease Control and Prevention (mean, 58.4 cases/yr; **Fig 1**).[48,a] Most of these cases (67%) were reported from California, where the disease is endemic and there has traditionally been heightened interest in surveillance. Between 1978 and 1986, a total of 228 cases were reported nationally (mean, 28.5 cases/yr).[49]

Although there have been no national seroprevalence studies in the United States, geographically limited investigations targeting specific populations and professional groups have been conducted. The highest seroprevalence has been found among persons who work with livestock, such as farmers, slaughterhouse workers, and veterinary staff. On the basis of the distribution of human cases reported throughout the United States, Q fever is assumed to be enzootic in livestock in this country. However, most studies of Q fever in animals have been of limited geographic scope, have focused on cattle rather than other reservoir species, and have documented the presence of antibodies rather than active infection.

Prevention

Although human and animal vaccines for Q fever have been developed, none are commercially available for use in the United States. Therefore, prevention efforts must focus on minimizing contact with animals that may be shedding *C burnetii*. Although it may not be practical or possible to eliminate the risk for Q fever in a typical farm setting, the risk for transmission can be decreased through attention to proper sanitation when dealing with parturient animals and ensuring proper pasteurization of milk products. In a research setting, prevention efforts should focus on acquiring and maintaining Q fever-free stock or on strict biocontainment of research animals.[50,51] Research institutions should also consider instituting serologic monitoring programs for employees and collecting and storing serum samples at the time of employment in order to document infections by change in serostatus.

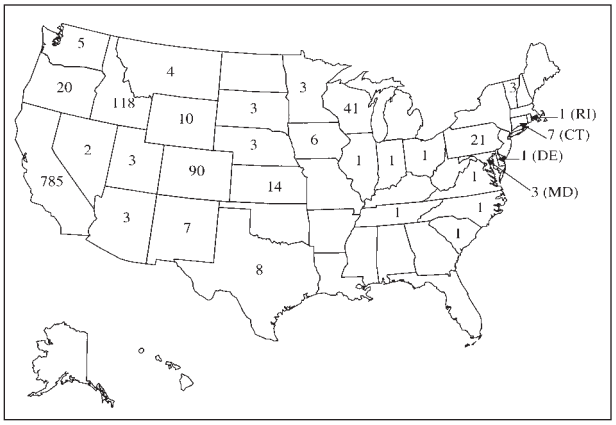

Figure 1—Q fever cases reported to the Centers for Disease Control and Prevention by state health departments, 1948 through 1977.[48]

Discussion

Although historically not perceived as an important public health threat in the medical or veterinary communities, *C burnetii* can cause debilitating disease and may result in potentially fatal chronic infections among humans. Although the disease is considered enzootic in the United States, human and animal *C burnetii* infections are underdiagnosed and underreported because of the protean nature of its clinical signs, the requirement for laboratory tests to establish a diagnosis, and the lack of awareness of this disease in the medical and veterinary communities.

Finally, *C burnetii* is considered a potential agent of bioterrorism because of its accessibility, low infectious dose, resistance to environmental degradation, and aerosol route of transmission.[52] Because national surveillance for Q fever is currently lacking in the United States, it would be difficult to detect and respond to a bioterrorism event involving *C burnetii*. Q fever was made nationally notifiable in humans in 1999, and although this represents a critical first step toward improved surveillance, the disease continues to be underreported in the United States. Additional improvements in surveillance, such as increasing physician reporting, making animal infections notifiable, and conducting systematic seroprevalence studies in both humans and animal populations, would provide important information.

[a]The number of cases (1,168) was derived from Figure 1 of reference 48. The case number reported in the text of this reference did not match the number presented in the map.

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