

Q Fever

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Q fever is a zoonotic disease caused by *Coxiella burnetii*, a species of bacteria that is spread to animals by ixodid (hard) ticks.

Bacteriology

C. burnetii is a small Gram-negative obligate intracellular parasite. It cannot reproduce outside their host cell; it replicates in host monocytes and macrophages. It is morphologically similar to coccoid or rod-shaped rickettsia with a cell wall similar to Gram-negative bacteria.

The bacterium has spore-like structures which enable the bacteria to remain tremendously stable and resistant to environmental conditions. It can survive for several weeks to months lying idle in the soil, capable of surviving standard disinfectants and resisting heating or drying. For example, it can survive seven to 10 days on wool at room temperature, one month on fresh meat in cold storage, 120 days in dust and more than 40 months in skim milk. *C. burnetii* is much more stable and resistant than other Rickettsiae.

Survival:	<i>Coxiella</i>	<i>Rickettsiae</i>
...at 60°C (140°F)	60 minutes	15 minutes
... in 0.5% Formalin	4 days	< 24 hours

C. burnetii is killed by pasteurization. There is only one serotype of *C. burnetii*.

Coxiella burnetii exists in two antigenic phase variations. This is important in the diagnosis and treatment of Q fever. Phase I is the smooth variation, pathogenic and found in infected animals or in nature. Phase I antigen is related to virulence and is antiphagocytic. Phase I has a cell wall-associated antigen that behaves as a capsule, masking the Phase II antigen. Phase II is recovered only after multiple pass-ages in eggs or cell/tissue cultures in a laboratory. Phase II antigens lack the surface Phase I antigen. Phase II is less pathogenic and is easily phagocytized even in absence of specific antiserum. Antibodies to Phase I antigens of *C. burnetii* generally require longer to appear and indicate continued exposure to the bacteria. Therefore, increased antibodies in a serum sample to Phase II antigens indicate acute cases while a rise in Phase I, reflects a chronic infection of Q fever.

Epidemiology

Infections have occurred worldwide since the organism was discovered in 1937. Infections can occur in a range of domestic and wild animals but are considered uncommon in the United States. A seroprevalence survey of IgG antibodies was conducted in the U.S. in 2003 to 2004. The 4,437 adult participant bloods came from the National Health and Nutrition Survey (NHANES). The tests used were ELISA assays with IFA confirmation; overall prevalence was 3.1%.

In 1999, Q fever became a nationally notifiable disease in humans in the U.S. due to the ability of the bacteria to be used as a weapon for bioterrorism. By reason that humans are generally very susceptible, very few organisms are required to cause infection and there is airborne transmission of the stable and envi-

ronmentally resistant bacteria. The World Health Organization (WHO) estimated that if Q fever was aerosolized in a city of approximately five million people, there would be 125,000 ill and 150 deaths; the agent could travel downwind for greater than 20 km.

Animal Reservoirs

The primary reservoirs are domestic livestock including sheep, goats and cattle. Dogs, cats, rabbits, horses, pigs, camels, buffalo, rodents, pigeons, geese and other fowl may also carry *C. burnetii*. Infections can occur in a range of domestic and wild animals but are considered uncommon in United States.

Animal Disease

Infections in animals are usually inapparent, 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 placentas, 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. In sheep, abortion can affect 5% to 50% of the flock. However, lambings subsequent to *Coxiella* abortions have been found to be carried to term. Ewes can remain chronically infective and continue to shed organisms in a carrier state.

The bacteria are excreted in milk, urine and feces of infected animals. During and several days after birthing, the bacteria are shed in high concentrations in the placenta/placental fluids. The incubation period for animals is variable. Sheep, goats and cattle may be infected by a tick bite, or via animal to animal transmission. Dogs and cats may be infected by consumption of placentas or milk from infected ruminants or by an aerosol route. Q fever infection in parturient dogs or cats may lead to early death of pups and kittens.

Information on the prevalence of disease in animal species is limited. In endemic areas, such as areas of California, it was found that 18% to 55% of sheep and up to 82% of cows in some dairy farms had antibodies to *C. burnetii*.

Animal products

Exposure to farm animals is NOT the only means of acquiring Q fever, especially now when people are often consuming un-pasteurized dairy products, there seems to be more possible cases.

Unpasteurized milk, goat cheese, fresh cheeses etc. (queso fresco) can be dietary sources. Cats can also be a source, especially if the cats are stray. Any animal in rural in many agricultural areas may be a source. The environment in areas where sheep and other ruminants are concentrated may also be a source. The disease may also be tick borne.

Transmission to Humans

Human infections are usually acquired after contact with infected ruminants, sheep, goats and cattle in particular, or their contaminated products. However, other animals, including cats, dogs and birds are occasionally associated with human infections.

Transmission usually occurs through inhalation of the bacteria in droplets or windborne dust contaminated by dried excreta or placenta/placental fluids. Consumption of unpasteurized dairy products may result in human infection. Contamination may occur through direct contact with infected animals and other contaminated materials such as wool, straw, fertilizer and laundry. In addition, direct transmission by blood or marrow transfusion has been reported.

Q fever is more common among veterinarians, meat-packing, rendering and stockyard workers, sheep and dairy workers and farmers. However, individual cases may occur where no direct animal contact can be demonstrated.

Humans are considered to be dead-end hosts and the only species known to regularly develop illness as a result of infection.

Human Disease Burden

Generally, there are sporadic cases with most reported outbreaks epidemiologically linked to enclosed environments among occupations with animals or their products of parturition, including meat packing houses, wool and hair processing plants. A few outbreaks have also been reported among persons residing in cities and towns downwind from sites where infected animals are kept. Human cases of Q fever have been reported from almost every state. However, reporting is not required in many other countries and hence, the disease is considered to be underreported with an unreliable reported number of cases occurring worldwide.

In 1944, there were outbreaks among British and American troops stationed in the Mediterranean (Italy), during World War II and during the Persian Gulf War (1990's).

Between the years 1948 to 1977, 1,168 cases of Q fever in humans were reported; most cases (67%) were reported from California. Between 1978 through 1999, 436 cases were reported by state health departments in the United States. There were no cases reported by Louisiana. During 2000 through 2004, the first five years in which Q fever was nationally reportable, 255 cases were reported from 37 states and the District of Columbia. Fifty percent of these cases were reported from March to June (the lambing season), although cases were reported throughout the year. Seventy-seven percent of cases were male, 92% were White, and the mean age at onset was 50.5 years. In 2001, there was one case reported in Louisiana. The average annual incidence in Louisiana per million persons is 0.07. It should be noted that epidemiologic data is limited due to the asymptomatic and self-limiting nature of most cases of the disease, thereby making the disease underreported.

The incubation period is approximately two to five weeks after exposure to *C. burnetii* (mean ~ 20 days). The length of incubation period is inversely proportional to the size of the dose or the number of organisms that initially infect the patient. As few as one organism is capable of causing disease.

The infectious dose is very small, A single, inhaled, organism may produce clinical illness. In [non-human] primates, the dose to kill 50% of the primates was found to be 1.7 organisms.

Clinical Description

About one-half of all people infected are asymptomatic.

Q fever can be very difficult to diagnose in its early stages, even by experienced physicians who are familiar with the disease. Patients infected with *C. burnetii* generally display a nonspecific clinical presentation which may resemble a variety of other infectious and non-infectious diseases. For example, patients with Q fever may show a transient thrombocytopenia.

Infections can lead to acute or chronic disease manifestations.

Acute infection: Characterized by sudden onset of fevers (greater than 100.5°F), severe headache, malaise, myalgia, confusion, sore throat, chills, sweats, non-productive cough, nausea, vomiting, diarrhea, abdominal pain, loss of appetite and chest pain. Approximately one-third of patients may develop acute respiratory disease (pneumonia), and up to two-thirds of patients may have hepatic involvement with abnormal results on liver function tests. Radiographs of patients with pneumonia manifestations resemble those of patients with viral pneumonia etiologies. Multiple rounded opacities of both lungs on x-ray may be noted. Pleural effusion may also be seen. Exanthema (rash) occurs in about 10% of cases. Rarely (<1%) meningoencephalitis or pericarditis may occur with acute infection. Most patients will recover to good health within several months without any treatment, as only 1% to 2% will require hospitalization or even die of the disease.

Chronic infection: Characterized by infection that persists for more than six months with manifestations including granulomatous hepatitis, osteomyelitis, or culture negative endocarditis. Approximately 10% of patients report symptoms of chronic fatigue for months to years after acute infection. Patients, who have had acute Q fever infection, may develop the chronic form as soon as one year or as long as 20 years after initial infection. Cases of chronic Q fever are extremely rare occurring in less than 1% of acute Q fever infected patients. Most cases often occur in patients with underlying valvular heart disease, 40% of those with valvular heart disease and acute Q fever. As many as 65% of persons with chronic Q fever may die of the disease.

Those whom recover fully from infection may possess lifelong immunity.

Pregnant women who become infected by *C. burnetii* are typically asymptomatic. However, the organism can be transplacentally transmitted. Depending on the timing of infection, resulting abortions or neonatal deaths, premature births, low birth weights or placentitis may occur. The greatest risk is during the first trimester. Women contracting Q fever also are at great risk of developing chronic Q fever infection. Pregnant women with Q fever can also pose a degree of risk to medical staff in contact with infected pregnant women.

Laboratory Tests

Serologic assays are the most widely available and frequently used methods for confirming cases of Q fever.

Isolation

C. burnetii can be isolated and identified in infected tissues by immunohistochemical staining and DNA detection methods (PCR) during the febrile period. Also, it can be recovered from blood, urine and semen. Because of the high risk of infection, attempts at isolation should be made only in specialized labs.

Serology

Prior to the 1990s, the complement fixation test was the most widely used serologic assay for diagnosing Q fever. Currently, the indirect immunofluorescence assay (IFA) is generally considered the standard and most dependable and widely used method in Q fever serology. IFA can be used to detect either IgG, IgM, or IgA antibodies. Blood samples taken early (acute), and late (convalescent) in the disease are the preferred specimens for evaluation.

- Most patients demonstrate increased IgM titers after the first week of illness.
- Diagnostic levels of IgG antibody generally do not appear until three weeks after the onset of illness.
- Antibodies may persist as long as 10 to 15 years detected by IFA

The value of testing two sequential serum samples together to show a rising antibody level is important in confirming acute and chronic infections.

C. burnetii exists in two antigenic phases called phase I and phase II. This antigenic difference is important in diagnosis. In acute cases of Q fever, the antibody level to phase II is usually higher than that to phase I, often by several orders of magnitude and generally is first detected during the second week of illness. In chronic Q fever, the reverse situation is true; the antibody level to phase I is usually higher than that to phase II (Table).

Table: Onset of *C. Burnetii* Phase I and Phase II.

Onset		7days	21-28days	30-60days	2-3 years	> 3 years
Acute – Phase II	IgM					
	IgG					Very low
Chronic – Phase I	IgM					
	IgG					

Antibodies to phase I antigens of *C. burnetii* generally require longer to appear and indicate continued exposure to the bacteria. Thus, high levels of antibody to phase I in later specimens in combination with constant or falling levels of phase II antibodies and other signs of inflammatory disease suggest chronic Q fever. Antibodies to phase I and II antigens have been known to persist for months or years after initial infection.

Combined detection of IgM, IgA and IgG improves the specificity of the assays and provides better accuracy in diagnosis. IgM levels are helpful in the determination of a recent infection. In acute Q fever, patients will have IgG antibodies to phase II and IgM antibodies to phases I and II. Increased IgG and IgA antibodies to phase I is often indicative of endocarditis and chronic Q fever.

Treatment

Doxycycline (100 mg for adults or 4 mg/kg/day in two divided doses for children under 45 kg [100 lbs]) is the drug of choice for patients with Q fever. Although, tetracyclines generally should not be given younger than eight years of age, most experts consider that the benefit of doxycycline in treating Q fever is greater than the potential of dental staining. Antibiotic treatment is most effective when initiated during the early phase of the illness; treatment should not be withheld for pending results of confirmatory tests within the first three days of illness. A dose taken orally twice daily for 15 to 21 days is a frequently prescribed therapy.

For chronic Q fever infections, two different treatment protocols have been recommended:

- 1) doxycycline in combination with quinolones for at least four years and
- 2) doxycycline in combination with hydroxychloroquine for 1.5 to three years

Doxycycline and quinolones are contraindicated in pregnant women but long term therapy with cotrimoxazole (trimethoprim/sulfamethoxazole combination) has prevented fetal death in some cases. Doxycycline in combination with hydroxychloroquine is recognized to lead to fewer relapses, but requires routine eye exams to detect accumulation of chloroquine.

Surveillance

Q fever is a Class A condition reportable within 24 hours of diagnosis.

Case Definition

Clinical description:

Asymptomatic infections may occur.

Acute infection: A febrile illness usually accompanied by myalgia, malaise and retrobulbar headache. Severe disease can include acute hepatitis, pneumonia and meningoencephalitis. Clinical laboratory findings may include elevated liver enzyme levels and abnormal chest film findings.

Chronic infection: Potentially fatal endocarditis may evolve months to years after acute infection, particularly in persons with underlying valvular disease. A chronic fatigue-like syndrome has been reported in some patients.

Laboratory criteria for diagnosis

- Fourfold or greater rise in antibody titer to *C. burnetii* phase II or phase I antigen by indirect immunofluorescence antibody (IFA) or complement fixation (CF) in acute- and convalescent-phase paired serum specimens ideally taken three to six weeks apart
- Or Isolation of *C. burnetii* from clinical specimen by culture
- Or Positive polymerase chain reaction assay to *C. burnetii*
- Or Demonstration of positive immunofluorescence of skin lesion (biopsy) or organ tissue (autopsy)

Case classification (according to Centers for Disease Control and Prevention (CDC) 1999 Case Definition)

Probable: a clinically compatible or epidemiologically linked case with a single supportive Immunoglobulin G (IgG) or Immunoglobulin M (IgM) titer.

Confirmed: a clinically compatible or epidemiologically linked case that is laboratory confirmed.

Investigation

The purpose of investigation is to identify cases, to confirm the diagnosis, to identify high risk areas of the state and to provide information to the communities involved.

- Upon receipt of a report of a case of Q fever, contact the physician and/or hospital to confirm the diagnosis.
 - If the diagnosis is based on symptoms, encourage the physician to obtain paired sera to be tested by serologic tests that yield more accurate diagnostic information (indirect fluorescent antibody the preferred method or complement fixation).
- Attempt to identify:
 - History of exposure to infected animals or animal products
 - History of travel
 - Occupation: occasional cases occur in industrial settings, related to the processing of batches of highly contaminated imported animal fibers, particularly goat hair
 - Farming

Prevention

In the U.S., Q fever outbreaks have resulted mainly from occupational exposure involving veterinarians, meat processing plant workers, sheep and dairy workers, livestock farmers and researchers at facilities housing sheep. Prevention and control efforts should be directed primarily toward these groups and environments.

The following measures should be used in the prevention and control of Q fever:

- Educate the public on sources of infection.
- Appropriately dispose of placenta, birth products, fetal membranes and aborted fetuses at facilities housing sheep and goats.
- Restrict access to barns and laboratories used in housing potentially infected animals.
- Use only pasteurized milk and milk products.
- Use appropriate procedures for bagging, autoclaving and washing of laboratory clothing.

- Vaccinate (where possible) individuals engaged in research with pregnant sheep or live *C. burnetii*.
- Quarantine imported animals.
- Ensure that holding facilities for sheep should be located away from populated areas. Animals should be routinely tested for antibodies to *C. burnetii* and measures should be implemented to prevent airflow to other occupied areas.
- Counsel persons at highest risk for developing chronic Q fever, especially persons with pre-existing cardiac valvular disease or individuals with vascular grafts.

A vaccine for Q fever has been developed and has successfully protected humans in occupational settings in Australia. However, this vaccine is not commercially available in the United States. Persons wishing to be vaccinated should first have a skin test to determine a history of previous exposure because severe reactions are possible. Individuals who have previously been exposed to *C. burnetii* should not receive the vaccine because severe reactions, localized to the area of the injected vaccine, may occur. A vaccine for use in animals has also been developed, but it is not available in the United States.

Hospital Precaution and Isolation: Standard precautions.