Slide 1

Q Fever

Query Fever
Coxiellosis

Slide 2

Overview

- Organism
- History
- Epidemiology
- Transmission
- Disease in Humans
- Disease in Animals
- Prevention and Control
- Actions to Take

In today's presentation we will cover information regarding the organism that causes Q Fever and its epidemiology. We will also talk briefly about the history of the disease, how it is transmitted and clinical disease in humans and animals. Finally, we will address prevention and control measures for Q fever.

[Photo: Sheep and lambs. Source: Stephen Ausmus/USDA ARS]

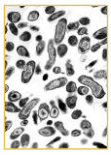
Slide 3

ORGANISM

Slide 4

The Organism

- *Coxiella burnetii*
  - Obligate intracellular pathogen
  - Proteobacteria
  - Stable and resistant
  - Killed by pasteurization
  - Two antigenic phases
    - Phase 1: virulent
    - Phase 2: less pathogenic



Coxiella burnetii is a obligate intracellular gram-negative pathogen. It was previously identified as a rickettsial agent, but has been recently reclassified as Proteobacteria, the same group that contains bacteria such as *Legionella*. It replicates in host monocytes and macrophages. It has tremendous stability and can reach high concentrations in animal environments. Because it forms unusual spore-like structures it is highly resistant to environmental conditions and many disinfectants. *Coxiella burnetii* can survive 7 to 10 days on wool at room temperature, 1 month on fresh meat in cold storage, 120 days in dust and more than 40 months in skim milk. The organism is killed by pasteurization. *Coxiella burnetii* exists in two antigenic phases. This is important in the diagnosis of Q fever. Phase I is pathogenic and found in infected animals or in nature. Phase II is less pathogenic and is recovered only after multiple lab passages in eggs or cell cultures. Increased antibodies to phase II antigens indicate acute infection while a rise in phase I reflects a chronic infection of Q fever.

[Photo: *Coxiella burnetii.* Source: National Institute of Allergy and Infectious Diseases/NIH at https://www.niaid.nih.gov/SiteCollectionImages/topics/biodefenserelated/QFEVER_1.JPG]

Slide 5

HISTORY

Slide 6

History

- 1935
  - Queensland, Australia (abattoir worker)
  - Montana, USA (ticks)
- Outbreaks
  - Military troops
    - When present in areas with infected animals
  - Cities and towns
    - Downwind from farms
    - By roads traveled by animals

Q "Query" fever was first reported in Brisbane, Queensland, Australia, in 1935 by Derrick, who described outbreaks of febrile illness in abattoir workers. Burnet and his associate Freeman successfully isolated the organism and investigated the epidemiology of the disease. Concurrently, a similar agent (initially called the "Nine Mile agent") was isolated from ticks in Montana by Davis and Cox and was subsequently found to be the same organism as that found in Queensland. In 1938 the organism was named *Coxiella burnetii* in honor of Cox and Burnet. In 1944 there were outbreaks among British and American troops stationed in the Mediterranean (Italy); outbreaks also occurred during World War II and during the Persian Gulf. Outbreaks have similarly been reported among persons residing in cities and towns downwind from sites where infected animals are kept.

[Photo: Ewes. Source: Danelle Bickett-Weddle/CFSPH]

Slide 7

TRANSMISSION

Slide 8

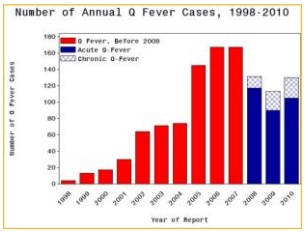
Transmission

- Aerosol
  - Parturient fluids
    - 10^9 bacteria released per gram of placenta
  - Urine, feces, milk
- Direct contact
- Fomites
- Ingestion
- Arthropods (ticks)

Aerosolization is the primary mode of transmission in humans and domestic ruminants represent the most frequent source of infection. Organisms can be found in airborne droplets or dust contaminated by placental tissues, birth fluids, or excreta of infected animals. Shedding of *C. burnetii* into the environment occurs mainly during parturition; over 10^9 bacteria per gram of placenta are released at the time of delivery. Aerosol or direct transmission can occur when infected animals are processed as meat, during necropsies, or while assisting deliveries. Due to persistence of the organism in the environment, dried infective material can contaminate water, dust, and soil; *C. burnetii* has been isolated downwind up to ½ mile or more from a known source. Fomites (i.e., newborn animals, wool, bedding, clothing) can also be contaminated and serve as a source of infection. Shedding in the milk occurs due to infected mammary glands, but pasteurization kills this organism. *C. burnetii* has been naturally and experimentally isolated from a variety of arthropods, (mainly ticks but

		also cockroaches, beetles, flies, fleas, lice, mites). Over 40 tick species are naturally infected with *C. burnetii*, and transovarial (mother to offspring) and transstadial (between developmental life stages) transmission has been documented. Feces of infected arthropods can serve as a source of *C. burnetii* infection and can remain infective for at least 19 months. Animals typically acquire Q fever through exposure to other infected animals, either through direct contact with contaminated material or aerosol exposure. [Photos: (Top) Ewe and lambs. Source: Stephen Ausmus/USDA ARS; (Bottom) *Dermacentor andersoni* tick. Source: Christopher Paddock/CDC]
Slide 9	Transmission • Person-to-person (rare) – Transplacental (congenital) – Blood transfusions – Bone marrow transplants – Intradermal inoculation – Possibly sexually transmitted	Person-to-person transmission is extremely rare. Transplacental transmission may occur resulting in congenital infection. Transmission from blood transfusions, bone marrow transplants, and intradermal inoculations have also been reported. Transmission via sexual intercourse has been hypothesized. Sexual transmission of *Coxiella burnetii* has been documented in mice and guinea pigs and hypothesized for a rare number of human cases.
Slide 10	**EPIDEMIOLOGY**	
Slide 11	Epidemiology • Worldwide – Except New Zealand • Reservoirs – Domestic animals • Sheep, cattle, goats, dogs, cats – Birds – Reptiles – Wildlife	Q fever is a zoonosis with worldwide distribution. It has been reported on all continents, except New Zealand, and is endemic in areas where reservoir animals are found. The animal reservoir is large and include many wild and domestic mammals, birds, and arthropods. However, the primary reservoirs are considered to be cattle, sheep, goats, and ticks. Wildlife species reported as reservoirs include snowshoe hares, moose and white-tailed deer in Nova Scotia, wild Dall sheep in Alaska, and black bears in Idaho and California.
Slide 12	Epidemiology • Occupational and environmental hazard – Farmers – Livestock producers – Veterinarians and technicians – Meat processors/ abattoir workers – Laboratory workers 	Q fever is an occupational hazard for persons in contact with domestic animals, such as cattle, sheep and goats. Persons at risk include farmers, livestock producers, veterinarians, abattoir workers, those in contact with dairy products, and laboratory personnel performing culture and diagnostics. There has been an increase in reports of sporadic cases in people living in urban areas after occasional contact with farm animals or after contact with infected pets, such as dogs and cats. [Photo: Lab pipetting. Source: CFSPH]

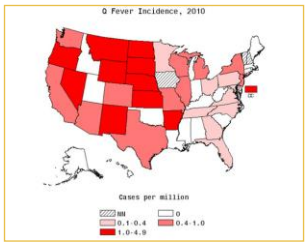
Slide 13



The graph displays the number of human cases of Q fever cases reported to CDC annually from 1998 through 2010. Cases of Q fever increased steadily from 13 cases in 1999 when the disease became nationally notifiable, to 167 cases in both 2006 and 2007. Cases decreased significantly in 2008 and 2009 with total cases at their lowest in 2009 (n=113) with a slight increase in 2010. Beginning in 2008, cases were differentiated as acute or chronic. Acute cases generally make up 80-90% of cases reported. [Source: Centers for Disease Control and Prevention. Q Fever at http://www.cdc.gov/qfever/stats/index.html]

Slide 14

Q Fever in the U.S., 2010



This figure shows the incidence of Q fever cases by state in 2010 per million persons. Q fever was not notifiable in Iowa, New Hampshire, and Vermont in 2010. The incidence rate was zero for Alabama, Alaska, Connecticut, Delaware, Hawaii, Idaho, Indiana, Kentucky, Louisiana, Maine, Massachusetts, Mississippi, Oklahoma, Rhode Island, South Carolina, Utah and West Virginia. Incidence ranged between 0.1 to 0.4 cases per million persons for Florida, Georgia, Maryland, Minnesota, North Carolina, Ohio, Pennsylvania, Tennessee and Virginia. Annual incidence ranged from 0.4 to 1.0 case per million persons in Arizona, California, Colorado, Illinois, Michigan, Missouri, New Jersey, New York, Texas, Washington, and Wisconsin. The highest incidence rates, ranging from 1.0 to 4.9 cases per million persons were found in Arkansas, the District of Columbia, Kansas, Montana, Nebraska, Nevada, New Mexico, North Dakota, Oregon, South Dakota and Wyoming. [Source: Centers for Disease Control and Prevention. Q Fever at http://www.cdc.gov/qfever/stats/index.html]

Slide 15

DISEASE IN HUMANS

Slide 16

Human Disease

- Incubation: 2 to 5 weeks
- One organism may cause disease
- Humans are dead-end hosts
- Disease
  - Asymptomatic (50%)
  - Acute
  - Chronic

In humans, the incubation period varies from 2 to 40 days (mean around 20 days). As few as one organism is capable of causing disease. Humans are considered to be dead end hosts and are the only species known to develop illness regularly as a result of infection. Most cases of Q fever are asymptomatic; only about 50% of all people infected with *C. burnetii* show signs of clinical illness. The two clinical forms of the disease are acute (less than 6 months duration) and chronic (greater than 6 months duration).

Slide 17

Acute Infection

- Flu-like, self limiting
- Atypical pneumonia (30 to 50%)
- Hepatitis
- Skin rash (10%)
- Other signs (< 1%)
  - Myocarditis, meningoencephalitis, pericarditis
- Death: 1 to 2%

Symptoms of acute disease can vary in severity and duration; a self-limited febrile or flu-like illness often occurs. Signs include fever, chills, "sweats", retrobulbar headache, fatigue, anorexia, malaise, myalgia, and chest pain. Illness typically lasts from one to three weeks. 30 to 50% of patients with symptomatic illness will develop pneumonia. In more severe cases, a nonproductive cough with pneumonitis may develop. Radiographs of patients with pneumonia resemble those of patients with viral pneumonia etiologies. Multiple rounded opacities of both lungs on x-ray may be noted, and pleural effusion may also be seen. Additionally, many clinically ill patients will have abnormal liver enzymes, and some will develop hepatitis although jaundice is rare. Exanthema (rash) occurs in about 10% of cases. Rarely meningoencephalitis or pericarditis may occur with acute infection. Only 2% of acute infections require hospitalization and a similar percentage result in death.

Slide 18

Chronic Disease

- 1 to 5% of those infected
  - Prior heart disease, pregnant women, immunocompromised
- Endocarditis
- Other
  - Granulomatous hepatitis
  - Cirrhosis
  - Osteomyelitis
- 50% relapse rate after antibiotic therapy

Chronic Q fever (infection greater than six months in duration) occurs in 1 to 5% of those infected and is relatively uncommon. It typically develops in persons with pre-existing cardiac valvular disease. Immunocompromised persons and pregnant women are also at great risk for the chronic form. Endocarditis is the major clinical presentation and accounts for 60 to 70% of all chronic Q fever cases. Infection can also affect the liver causing granulomatous hepatitis or cirrhosis. Kupffer cells are considered to be target cells for *C. burnetii*. Involvement in bone and arteries has also been reported. Patients who have had acute Q fever may also develop the chronic form as soon as 1 year or as long as 20 years after initial infection.

Slide 19

Risk to Pregnant Women

- Most asymptomatic
- Transplacental transmission
- Reported complications
  - In-utero death
  - Premature birth
  - Low birth weight
  - Placentitis

Pregnant women who become infected by *C. burnetii* are typically asymptomatic. However, the organism can be transplacentally transmitted. Depending on the timing of infection abortion, neonatal death, premature birth, low birth weight, or placentitis may occur. The greatest risk is during the first trimester. Pregnant women are also at a greater risk of developing chronic Q fever infection. Pregnant women with Q fever may pose a degree of risk to medical staff.

Slide 20

Prognosis

- Usually self-limiting
- Only 2% develop severe disease
- Active chronic disease
  - Usually fatal if left untreated
  - Fatality for endocarditis: 45 to 65%
  - 50 to 60% need valve replacement
- Case-fatality rate: <1 to 2.4%

Q fever is usually a self-limiting illness and most cases resolve within 2 days to 2 weeks. Approximately 50 to 60% of cases are thought to be asymptomatic, and complications from the acute form of disease are rare. Only 2% of persons infected with *Coxiella burnetii* develop severe disease and require hospitalization. In general, the mortality rate is 1% or lower if treated. Active chronic disease is usually fatal if untreated. In patients with endocarditis, the fatality rate can range from 45 to 65%; additionally, 50 to 60% need valve replacement surgery. Because severe disease is rare the overall case-fatality rate for Q fever ranges from <1 to 2.4%.

Slide 21

Diagnosis

- Serology (rise in titer)
  - IFA, CF, ELISA, microagglutination
- DNA detection methods
  - PCR
- Isolation of organism
  - Risk to laboratory personnel
  - Rarely done

In humans, Q fever is usually diagnosed by serology (rise in antibody titer levels) which can be done as early as the second week of illness. There are a variety of serological tests for Q fever including IFA (immunofluorescence assay), CF (complement fixation), ELISA (enzyme-linked immunosorbant assay), and microagglutination. The indirect IFA is the most dependable and widely used method. *C. burnetii* may also be identified in infected tissue by IHC (immunohistochemistry) and DNA detection methods (PCR-polymerase chain reaction). Isolation of the organism is rarely done due to the risk *C. burnetii* poses for laboratory personnel. Clinical signs and patient history can also aid in diagnosis.

Slide 22

Treatment

- Treatment
  - Doxycycline
  - Chronic disease – long course
    - 2 to 3 years of medication
- Immunity
  - Long lasting (possibly lifelong)

The antibiotic treatment of choice is doxycycline. Antibiotic treatment is most effective when initiated within the first three days of illness. For chronic disease, treatment may be necessary for 2 to 3 years. Doxycycline and quinolones are contraindicated in pregnant women but long term therapy with co-trimoxazole (trimethoprim/sulfamethoxazole combination) has prevented fetal death in some cases. Persons recovering from Q fever are thought to develop long-lasting (possibly lifelong) immunity.

Slide 23

Dairy Farmer Case

- Male dairy farmer
  - Age 46
  - Sudden onset of fever, chills, cough
  - Initially diagnosed as influenza
  - Symptoms persisted for 2 weeks
  - Presented to emergency room
  - Again diagnosed as influenza

Now let's look at a few case studies of Q fever. A 46 year old male dairy farmer from Georgia reported a sudden onset of fever, chills, cough, and weight loss. A physician initially diagnosed influenza in the patient. Two weeks later the symptoms still persisted and the patient presented to the emergency room where he was again diagnosed with influenza. [Photo: Dairy calves. Source: Danelle Bickett-Weddle/CFSPH]

Slide 24

Dairy Farmer Case

- Referral to infectious disease specialist
  - Tested positive for Q fever
  - Antibiotics for 5 days
  - Resolved in 2 weeks
- Epidemiology
  - No recent calvings on his farm
  - Two beef cattle herds across the road
    - 2 out of 14 tested positive for Q fever

The emergency room doctor then referred the patient to an infectious disease specialist. The infectious disease specialist tested the patient for Q fever and he was positive. The patient took a five day course of a fluoroquinolone and symptoms resolved within 2 weeks. Although the patient owned several dairy cows, no recent calvings had occurred at his farm. Two beef cattle herds (approximately 35 animals per herd) were pastured across the road from the patient's farm. Fourteen animals from the neighboring beef herds were then tested; two animals were found to be positive for Q fever. [Source: *MMWR* October 18, 2002/51(41);924-927]

Slide 25

Urban Outbreak Case

- 1985, Nova Scotia, Canada
  - 33 cases of Q fever
    - 25 were exposed to cat
    - 17 developed cough
    - 14 developed pneumonia
  - Symptoms
    - Fever, sweats, chills, fatigue, myalgia, headache
  - Cat tested positive for *C. burnetii*

In 1985, a cluster of Q fever cases occurred in Nova Scotia, Canada. Most of the affected persons had symptoms of fever, sweats, chills, fatigue, myalgia and headache. Seventeen of the patients developed a cough and 14 had pneumonia. Epidemiological investigation revealed that 25 patients were exposed to a cat that had given birth to stillborn kittens 2 weeks prior. The majority of human cases lived or worked in 4 buildings near the apartment where the cat lived, and the cat visited the other buildings frequently. The cat tested positive for antibodies to *C. burnetii*. All human patients recovered uneventfully.

Slide 26

ANIMALS AND Q FEVER

Slide 27

Animal Disease

- Sheep, cattle, goats
  - May be asymptomatic
  - Reproductive failure
    - Abortions
    - Stillbirths
    - Retained placenta
    - Infertility
    - Weak newborns
    - Low birth weights
  - Carrier state

Sheep, cattle, and goats are the most common reservoirs of Q fever. The incubation period for animals is variable. Affected animals may be asymptomatic; when clinical disease occurs, reproductive failure is usually the only symptom seen. This may include abortions, stillbirths, retained placentas, infertility, weak newborns, and mastitis in dairy cattle. Lambs born following *Coxiella* abortions may be carried to term. However, ewes can remain chronically infected and continue to shed organisms. Organisms may be shed in milk and feces for several days after parturition.

[Photos: (Top) Sheep and goats. Source: USDA NRCS; (Bottom) Cow and calf. Source: Renee Dewell/CFSPH]

Slide 28

Animal Disease

- Other animal species
  - Dogs, cats, horses, pigs
  - Most other mammals
  - Fowl species
- Often asymptomatic
- Reproductive failure may occur

Dogs, cats, horses, pigs, and most mammals and fowl species may carry *C. burnetii*. Animals may be infected by a tick bite, consumption of placentas or milk from infected ruminants, or by the aerosol route. Most infections are asymptomatic; however, the most symptoms are related to reproductive failure. Still births and weak offspring are commonly reported.

Slide 29

Post Mortem Lesions

- Placentitis
  - Leathery and thickened
  - Purulent exudate
    - Edges of cotyledons
    - Intercotyledonary areas
- Aborted fetus
  - Non-specific

Placentitis is the most characteristic lesion in ruminants. The placenta is typically leathery and thickened. It may contain large amounts of creamy, white-yellow exudate at the edges of cotyledons and in the intercotyledonary area. Lesions in aborted fetuses are usually non-specific.

[Photo: Goat, placenta. The intercotyledonary placenta is thickened, opaque, and multifocally covered by tan clumps of exudate. Margins of several cotyledons are tan (necrosis), and centers are mottled red-brown (congestion and exudation). Source: Dr. J. Arzt/Plum Island Animal Disease Center/CFSPH]

Slide 30

Diagnosis and Treatment

- Diagnosis
  - Identification of organism
  - PCR
  - Serologic tests: IFA, ELISA, CF
  - Isolation of organism
    - Hazardous - Biosafety level 3
- Treatment
  - Tetracycline prior to parturition

C. burnetii can be detected in vaginal discharges, the placenta or its fluids, aborted fetuses, milk, urine and feces. Organism identification can be accomplished with Modified Ziehl-Neelson or Gimenez stains, but are usually not detected by Gram stain. IHC can also confirm bacterial identity. PCR techniques are also available in some laboratories. A number of serological tests are also available (i.e., immunofluorescence (IFA), enzyme-linked immunosorbent assays (ELISA) and complement fixation (CF). The complement fixation test is done most commonly. Although isolation of the organism can be accomplished in a variety of methods, it is dangerous to laboratory personnel, and must be completed in a Biosafety-Level 3 laboratory. It is therefore rarely used.

Little is known about the effectiveness of treating animals with antibiotics. Tetracycline has been given in water in the weeks preceding parturition in enzootic herds. This is believed to help reduce shedding in birthing materials. Antimicrobial therapy may not eradicate the "carrier" state of *C. burnetii* infection, but may suppress the number of abortion.

Slide 31

Morbidity and Mortality

- Prevalence unknown
- Endemic areas
  - 18 to 55% of sheep with antibodies
  - 82% of dairy cattle
- Morbidity in sheep: 5 to 50%
- Death is rare

Information on the prevalence of Q fever in animal species is limited. In endemic areas, (i.e. areas of California), it was found that 18 to 55% of sheep and up to 82% of cows in some dairies had antibodies to *C. burnetii*. In sheep, abortion can affect 5 to 50% of the flock. Death is rare in naturally occurring infections.

Slide 32

PREVENTION AND CONTROL

Slide 33

Prevention and Control

- Good husbandry
  - Tick prevention
  - Disposal of birth products
- Separate new or sick animals
- Vaccination
  - Human and animal
  - Not available in U.S.

Good husbandry plays an important role in the prevention and control of this disease. Tick prevention should be used to help prevent the spread of this disease. Animals that are about to give birth should be separated from the rest of the herd. Fetal membranes and aborted fetuses should be disposed of immediately either by burying or burning. New or sick animals should be separated from the rest of the herd until it can be determined that the animals are not contagious or do not pose an infectious risk. Vaccinations for humans and animals have been developed for this disease. However, they are not currently licensed for use in the United States.

Slide 34

Prevention and Control

- Pasteurization
- Disinfection
  - 10% bleach
- Eradication not practical
  - Too many reservoirs
  - Constant exposure
  - Stability of agent in environment

Pasteurization of milk from cows, sheep, and goats is important in stopping the spread of Q fever by contaminated milk sources. The amount of *C. burnetii* in the environment can be greatly reduced by thorough cleaning. A 10% bleach solution should be used to disinfect areas after cleaning where animals give birth. Eradication is impossible because of environmental stability, infectivity for wild animals, asymptomatic and carrier state in animals and people, and arthropods.

[Photo: Glass of milk. Source: H. Zell/Wikimedia Creative Commons at http://commons.wikimedia.org/wiki/File:Milk_001.JPG]

Slide 35

Q Fever as a Biological Weapon

- Accessibility
- Low infectious dose
- Stable in the environment
- Aerosol transmission
- WHO estimate
  - 5 kg agent released on 5 million persons
    - 125,000 ill - 150 deaths
    - Could travel downwind for over 20 km

Because of its highly infectious nature, stability in the environment, and aerosol route of transmission, *C. burnetii* can be considered a potential agent of bioterrorism. Although overall mortality associated with the disease is low, it could be considered a debilitating agent. The World Health Organization (WHO) estimated that if Q fever was aerosolized in a city of approximately 5 million people there would be 125,000 ill and 150 deaths. They estimated that the agent could travel downwind for greater than 20 km.

Slide 36

Additional Resources

- World Organization for Animal Health (OIE)
  - www.oie.int
- U.S. Department of Agriculture (USDA)
  - www.aphis.usda.gov
- Center for Food Security and Public Health
  - www.cfsph.iastate.edu
- USAHA Foreign Animal Diseases ("The Gray Book")
  - www.usaha.org/Portals/6/Publications/FAD.pdf

Slide 37

Acknowledgments

Development of this presentation was made possible through grants provided to the Center for Food Security and Public Health at Iowa State University, College of Veterinary Medicine from the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the Iowa Homeland Security and Emergency Management Division, and the Multi-State Partnership for Security in Agriculture.

Authors: Radford Davis, DVM, MPH; Glenda Dvorak, DVM, MS, MPH, DACVPM; Ann Peters, DVM, MPH
Reviewers: Kerry Leedom Larson, DVM, MPH, PhD

Last updated: March 2011