Q Fever — Human Health Implications

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Q fever — a history

- Febrile illness among abattoir workers in Brisbane, Queensland, Australia in 1935
- Only abattoir in Brisbane that slaughtered pregnant animals
- Q(ueury) fever
Q fever

- Obligate intracellular bacterium – *Coxiella burnetii*
- Occurs all over the world
  - Thought to be everywhere except New Zealand
- Highly infectious
  - As few as one organism can initiate an infection
Most human cases are thought to come from inhalation of aerosolized animal waste products

Main reservoirs = ruminants
Q Fever is a flu-like sickness caused by the germ *Coxiella burnetii*. Goats, sheep, cows, and other animals carry the germ.

Animals spread the germ when they give birth. People who help animals give birth, such as farmers and veterinarians, have a higher chance of getting Q Fever.

Wind can carry barnyard dust mixed with Q Fever germs for miles. You may get sick when you breathe in this dust, even if you aren’t around animals.
C. burnetii has been detected in a wide range of hosts
U.S. animal genotypes

ST20

ST8

ST16/26

Slide courtesy of Anne Straily: Photo Credits:
goat - http://ww2.valdosta.edu/~sibihl/goat.jpg
sheep - https://upload.wikimedia.org/wikipedia/commons/c/c4/Lleyn_sheep.jpg
Majority of U.S. human cases
Coxiella burnetii as a bioweapon

- Category B agent – causes moderate morbidity and mortality
- Highly infectious – as few as 1 organism may cause disease
- Highly resistant to heat, desiccation, and many disinfectants
- Can be aerosolized
Q Fever in Humans
Acute and Chronic Q Fever

- Q fever has both acute and chronic stages
- Acute
  - Incubation period = 2–3 weeks

- Chronic (aka persistent infection with *C. burnetii*)
  - Rare, estimated to occur in <5% of persons with acute infection
  - Can develop months to years after initial infection
  - High risk groups: pregnant women, immunocompromised, patients with existing valvulopathy or vascular defects
Clinical presentation of acute Q fever

- ~50% are asymptomatic
- Fever, fatigue, chills, and myalgia are the most common symptoms
- Severe headache is another common presentation
- Other observed symptoms
  - Cough
  - Rash
  - Hepatitis
  - Vomiting
  - Diarrhea
- Pneumonia is often associated with Q fever
- Median duration of untreated fever is 10 days
- Death: 1-2%
Acute Q fever treatment

- Most cases of acute Q fever will recover without antibiotic treatment
- Doxycycline for 14 days
What about prophylaxis for acute Q fever patients with identified risk factors for persistent infection?

- Jury is still out on this one; disagreement in the literature.
- Q researchers in the Netherlands
  - 134 patients with no antibiotic prophylaxis did not develop endocarditis.
  - The harm of low-threshold administration of long-term antibiotic prophylaxis might outweigh the benefit.
- Q researchers in France
  - 12-month prophylactic course of doxycycline and hydroxychloroquine protected at risk patients.
  - Conversely, all patients with significant valvulopathy but without any antibiotic prophylaxis evolved to endocarditis within few months.


Million M, Walter G, Thuny F, Habib G, Raoult D. Evolution from acute C fever to endocarditis is associated with underlying valvulopathy and age and can be prevented by prolonged antibiotic treatment, Clin Infect Dis, 2013, vol. 57 (pg. 836-44)
Clinical presentation of chronic Q fever

- Results from a persistent, focalized infection with *C. burnetii*
- Most cases present as blood culture negative endocarditis
- Other presentations include:
  - Vascular infections
  - Osteoarticular infections – more common in children
Q fever endocarditis

- Patients with pre-existing damage to native cardiac valve or prosthetic valve at increased risk
- Symptoms may include isolated relapsing fever, chills, night sweats, weight loss, and hepatosplenomegaly
- Difficult to diagnose
  - Routine blood cultures negative
  - Vegetative lesions rarely identified on echocardiogram
  - Requires index of suspicion, confirmation with specific laboratory testing
- Untreated Q fever endocarditis is fatal
Endocarditis = an infection of the inner lining of the heart and heart valves.
Endovascular Q fever infection

- Infection of arterial aneurysms or vascular grafts
- Develops more slowly in grafts than aneurysms
- High mortality rate even in treated patients
- Death most commonly caused by vascular rupture
Pediatric chronic Q fever infection

- Rarely reported
- Most frequently a chronic relapsing or multifocal osteomyelitis
  - Prolonged course with recurrent episodes affecting multiple bones

Figure 1 from Khatami, A, Sparks, RT, & Marais, BJ (2015). A Case of Pediatric Q Fever Osteomyelitis Managed Without Antibiotics. Ped 136: e1629–e1631
Treatment of chronic Q fever

- Remove nidus of infection when possible
- Combination therapy: doxycycline and hydroxychloroquine
  - Both can cause photohypersensitivity
  - Hydroxychloroquine can be toxic to the retina
- Minimum duration of therapy 18–24 months
  - Treat until 4-fold decrease in phase I IgG and complete disappearance of phase II IgM
- Monitoring of therapy
  - Monthly clinical evaluations
  - Monthly serologic testing
  - Monthly monitoring of drug plasma levels if no clinical response
- Limited data available of treatment in children
FIGURE. Q fever management algorithm

**Acute**

If a patient has clinical evidence of acute Q fever infection (e.g., fever, headache, rigor, weight loss, myalgia, anorexia, pneumonia, or hepatitis), and acute Q fever is suspected, perform diagnostic testing and initiate empiric treatment with doxycycline. Do not wait for laboratory results to begin treatment and do not stop treatment based on negative acute serology results.

Patient has any one of the following laboratory findings that indicate acute Q fever infection:
- Fourfold increase in phase II IgG or IgM antibody titer by IFA test in paired serum samples
- Convalescent phase II IgG antibody titer by IFA of >1:128
- Detection of DNA in a clinical specimen by PCR assay
- IHC staining of organism in a clinical specimen
- Isolation of Coxiella burnetii from a clinical specimen by culture

Perform clinical evaluation to determine whether patient is at high risk for chronic disease (e.g., heart valve or vascular defect).

- No risk
  - Repeat clinical assessment and serology in approximately 6 months.
  - To chronic algorithm
- Risk identified
  - Repeat clinical assessment and serology at 3, 6, 12, 18, and 24 months.
  - Consult a Q fever expert.

**Chronic**

Patient has clinical evidence of chronic Q fever infection with organ involvement and/or laboratory evidence of chronic Q fever infection:
- Demonstration of phase I IgG antibody titer by IFA ≥ 1:1024 or
- Detection of DNA in a clinical specimen (e.g., heart valve or serum) by PCR assay or
- IHC staining of organism in a clinical specimen (e.g., heart valve); or
- Isolation of Coxiella burnetii from a clinical specimen by culture

Not a case unless clinical and laboratory evidence are present (see Pregnancy section for exception). Continue serologic and clinical monitoring. If nonspecific clinical findings are present with laboratory evidence, perform a thorough search for site of infection (e.g., echocardiogram and PET/CT scan).

Chronic Q fever case
- Treat appropriately (minimum 18 months [native valves] and 24 months [prosthetic valves] for endocarditis; monitor clinically and serologically throughout treatment.
  - Serologic monitoring demonstrates fourfold decrease in phase I IgG with complete disappearance of phase II IgM and clinical recovery.
  - Discontinue antibiotic treatment and continue twice yearly serologic monitoring for potential relapse (minimum 5 years).
Q fever seroprevalence — a reminder to use caution when interpreting a single serology titer

- United States
  - 3.1% in samples taken in 2003–2004
- Netherlands
  - 12.2% in 2009
- New South Wales, Australia
  - 7% in samples taken 2006–2009
- Northern Turkey
  - 13.5% in 2006
- Chiang Mai region, Thailand
  - 25%
Occupational Exposure
Occupations with increased animal contact or contact with animal products are at highest risk.

- Veterinarians
- Butchers
- Dairy
- Slaughterhouse workers
- Farmers and ranchers
- Laboratory workers
- Wool or felt plant workers
- Tannery or rendering plant workers
Military personnel are an emerging at-risk group.
Q fever seropositivity in veterinarians

- 22% of veterinarians in U.S.
- 59% in small ruminant veterinarians in Ontario
- 45% in all categories of vets and 58% in livestock vets in southern Belgium
- 65% in livestock veterinarians in the Netherlands
- 14% in veterinarians in Japan
Potential control measures for workplaces with high exposure risk

- Educational training
- Medical surveillance
- Engineering controls
- Use of PPE
- Prophylaxis is not recommend
New Q fever factsheets

- English
- Spanish
- Arabic
- French
- Vietnamese
- Simplified Chinese
PPE to wear when working with an infected herd/flock

- Properly fitted respirator mask (e.g. N95)
- Eye protection
- Disposable gloves
- Coveralls
- Rubber boots or dedicated footwear
Activities where PPE is recommended

- Assisting with birthing
- Handling birth products
- Moving livestock
- Moving bedding material
- Cleaning barns or animal areas
- Working with manure and compost piles

Photo credit: Dr. J. Arzt, PIADC and Center for Food Security and Public Health at Iowa State University, College of Veterinary Medicine
We need your help!

- Survey of large animal clinical practitioners across the United States
- Goal = to understand the circumstances and challenges large animal veterinarians experience when working up an abortion event in livestock
- To access the survey, please visit: http://j.mp/2E2yjBE
Q fever National Surveillance
Q fever is part of the National Notifiable Diseases Surveillance System.

- Council of State and Territorial Epidemiologists and CDC Program Experts collaborate to determine which conditions are nationally notifiable.
- Health departments voluntarily submit infectious disease data to CDC.
- Goal = monitor, control, and prevent the occurrence and spread of these diseases and conditions.
Q fever surveillance in the United States

- National surveillance began in 1999 to better identify outbreaks related to bioterrorism.
  - No differentiation between acute and chronic cases.
- Chronic Q fever added to case definition in 2007.
- State and local health departments report cases of Q fever to CDC
  - National Notifiable Disease Surveillance System
  - Case report forms (CRFs)
Q fever Surveillance
Q fever Surveillance
Q fever Surveillance
Q fever Surveillance
Q fever Surveillance
Acute Q fever surveillance case definition

- Requires both clinical and laboratory evidence
- Clinical evidence
  - Any reported **fever and one or more of the following:**
    - rigors, severe retrobulbar headache, acute hepatitis, pneumonia, or elevated liver enzyme levels.
- Laboratory evidence
  - Must be supportive or confirmatory
  - Types of diagnostic tests available include:
    - Immunofluorescent assay (IFA)
    - Enzyme-linked immunosorbent assay (ELISA)
    - Polymerase chain reaction (PCR)
    - Immunohistochemistry (IHC)
    - Culture
Chronic Q fever surveillance case definition

- Requires both clinical and laboratory evidence
- Clinical evidence = **1 of the following conditions** in the absence of other known etiology.
  - Newly recognized, culture-negative endocarditis
  - Suspected infection of a vascular aneurysm or vascular prosthesis
  - Chronic hepatitis
  - Osteomyelitis/osteoarthritis
  - Pneumonitis
- Laboratory evidence: Must be supportive or confirmatory
  - Types of diagnostic tests available include:
    - Immunofluorescent assay (IFA)
    - Enzyme-linked immunosorbent assay (ELISA)
    - Polymerase chain reaction (PCR)
    - Immunohistochemistry (IHC)
    - Culture
C. burnetii phase variations — the confusing world of Q fever serology.

- Two distinct antigenic phase variations
  - Phase I is the virulent, highly infectious form that undergoes transition to
  - Phase II the avirulent during serial lab passages in embryonated eggs or cell culture.

YET
- Acute infection = Phase II appears first and is higher than phase I.
- Chronic infection = Phase I is high as may be phase II.
- Antibody response to phase variations is used to distinguish acute and chronic disease forms.

Lasciate ogne speranza, voi ch'intrate
Acute Q laboratory evidence

- **Supportive**
  - Single supportive IFA IgG titer of $\geq 1:128$ to phase II antigen, OR
  - Elevated phase II IgG or immunoglobulin M (IgM) antibody reactive with C. burnetii antigen by enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or latex agglutination.

- **Confirmed**
  - Fourfold change in ph II IgG antibody titer by IFA in paired serum samples OR
  - Detection of *C. burnetii* DNA by PCR assay, OR
  - Demonstration of *C. burnetii* in a clinical specimen by IHC methods, OR
  - Isolation of *C. burnetii* in cell culture
Chronic Q laboratory evidence

- **Supportive**
  - IgG antibody titer to *C. burnetii* phase I antigen ≥ 128 and < 800

- **Confirmed**
  - Serological evidence of IgG antibody to *C. burnetii* phase I antigen ≥ 1:800 by IFA (phase I titer must be higher than the phase II titer), OR
  - Detection of *C. burnetii* DNA by PCR assay, OR
  - Demonstration of *C. burnetii* in a clinical specimen by IHC methods, OR
  - Isolation of *C. burnetii* in cell culture
There’s a hole in our chronic Q fever case definition!

- Requirement of Ph 1 > Ph 2
- Patients with appropriate clinical manifestations and Ph 2 > Ph 1 or Ph 1 = Ph 2 fail to meet case definition

So where did the idea that Ph 1 > Ph 2 come from?
What do the Dutch have to say about this?

Table 1 from van der Hoek, W et al. (2011) Follow-up of 686 patients with acute Q fever and detection of chronic infection. Clin Infect Dis 52:1431 -1436.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age</th>
<th>Serology at 3 months</th>
<th>Serology at 6 months</th>
<th>Serology at 12 months</th>
<th>Known clinical risk factor at time of diagnosis acute Q fever</th>
<th>Clinical signs at follow-up</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>75</td>
<td>1.128</td>
<td>1.4096</td>
<td>1.8192</td>
<td>1.32768</td>
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<td>Endocarditis At 7 months</td>
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<td>1.16384</td>
<td>1.32768</td>
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<td>Endocarditis At 1 month</td>
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<tr>
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<td>1.1024</td>
<td>1.4096</td>
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<td>1.1024</td>
<td>Vascular disease</td>
<td>Infected aneurysm At 14 months</td>
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<td>na</td>
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<td>Persistent fever, At 15 months nummular eczema</td>
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<td>63</td>
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<td>1.1024</td>
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<td>None At 12 months</td>
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<tr>
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<td>None No treatment</td>
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<tr>
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<td>1.65536</td>
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<td>1.16384</td>
<td>Negative</td>
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<td>61</td>
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<td>1.65536</td>
<td>1.256</td>
<td>1.4096</td>
<td>Negative</td>
<td>Cardiac valve disease None At 3 months</td>
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<tr>
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<td>1.2048</td>
<td>1.4096</td>
<td>1.2048</td>
<td>1.16384 At 6 months</td>
<td>Unknown No treatment</td>
</tr>
</tbody>
</table>

NOTE: na, no serum samples available; undet, undetermined Ct value.
What does commercial Q testing in the United States show?

Number of annual Q fever cases 2000–2017
Q fever Surveillance Summary — United States, 2000–2012

- Acute Q — male to female ratio is 3:1
- Chronic Q — male to female ratio is 3.7:1
- >70% of reported patients were ≥ 40 years old
- 2.1% case fatality rate
  - No fatalities among cases < 40 years old
- 62% hospitalization rate

Geographic divisions with highest incidence rates.
Occupations of Cases Reported to National Surveillance

- 72% of reported Q fever cases are NOT in high risk occupations
- Top 5 Occupations listed
  - Unknown 33.8%
  - Rancher 17.7%
  - Military 8.4%
  - Retired 8.4%
  - Farm 4.6%
- Only 39% of reported Q fever cases had exposure to cattle, goats, or sheep

Frequency of reported cases of Q fever versus month of onset of symptoms — National Notifiable Disease Surveillance System.

Reported incidence rate of Q fever per million persons per year by age group — Acute Q Fever, 2008–2012.

Reported incidence rate of Q fever per million persons per year by age group — Chronic Q Fever, 2008–2012.

Resources


- MMWR. Diagnosis and Management of Q Fever — United States, 2013: Recommendations from CDC and the Q Fever Working Group. Available at: https://www.cdc.gov/mmwr/pdf/rr/rr6203.pdf


- CDC Q Fever website: https://www.cdc.gov/qfever/index.html
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.