Q Fever —Human Health Implications

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Q fever — a history

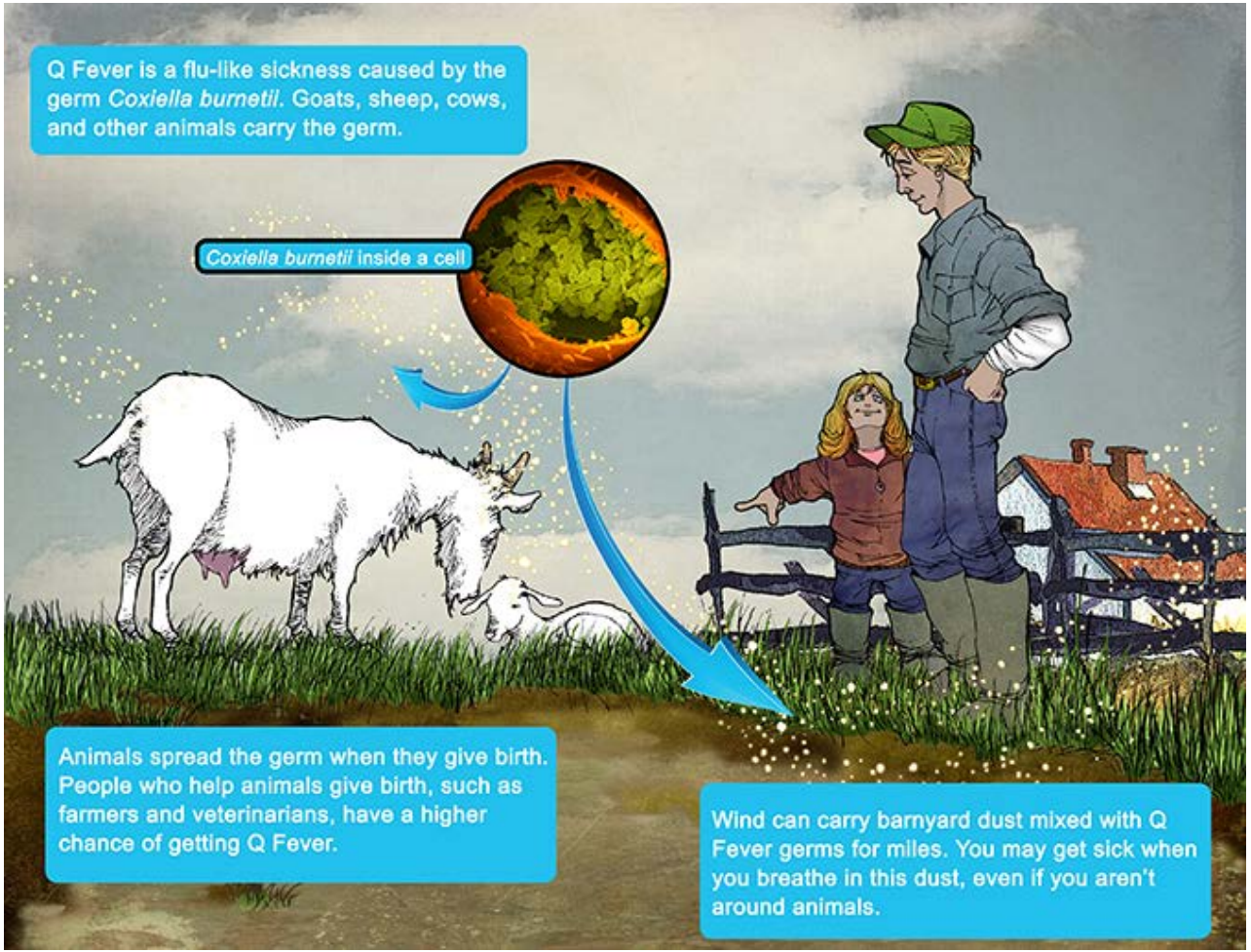
- Febrile illness among abattoir workers in Brisbane, Queensland, Australia in 1935
- Only abattoir in Brisbane that slaughtered pregnant animals
- **Q**(uery) fever

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.
Coxiella burnetii inside a cell
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:
cow - http://cdn.modernfarmer.com/wp-content/uploads/2014/09/cowhero2.jpg
goat - http://ww2.valdosta.edu/~slbihl/goat.jpg
sheep - https://upload.wikimedia.org/wikipedia/commons/c/c4/Lleyn_sheep.jpg

Majority of U.S. human cases

ST20

ST8

ST16/26

Slide courtesy of Anne Straily: Photo Credits:
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sheep - https://upload.wikimedia.org/wikipedia/commons/c/c4/Lleyn_sheep.jpg

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.

Limonard GJ, Nabuurs-Franssen MH, Dekhuijzen PN, Groot CA. Prevention of Q fever endocarditis, Lancet Infect Dis , 2011, vol. 11 (pg. 82-3)

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)

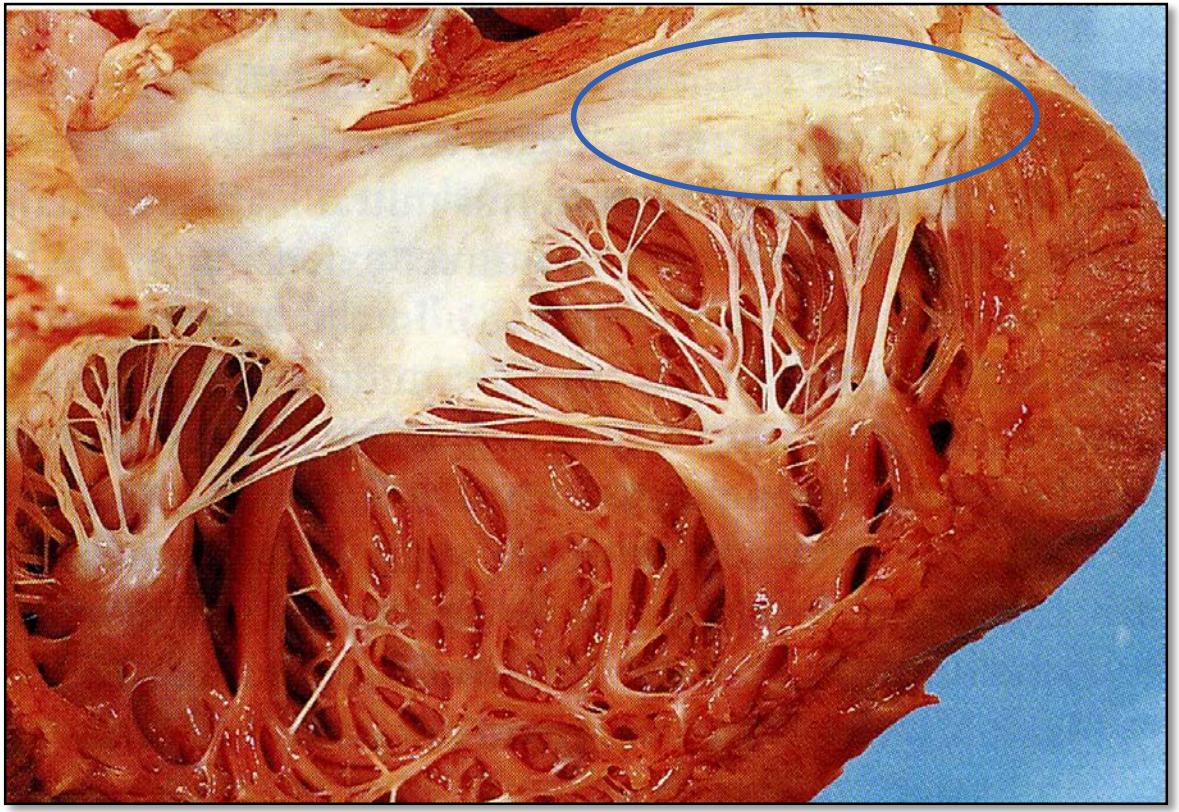
Clinical presentation of chronic Q fever

- 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

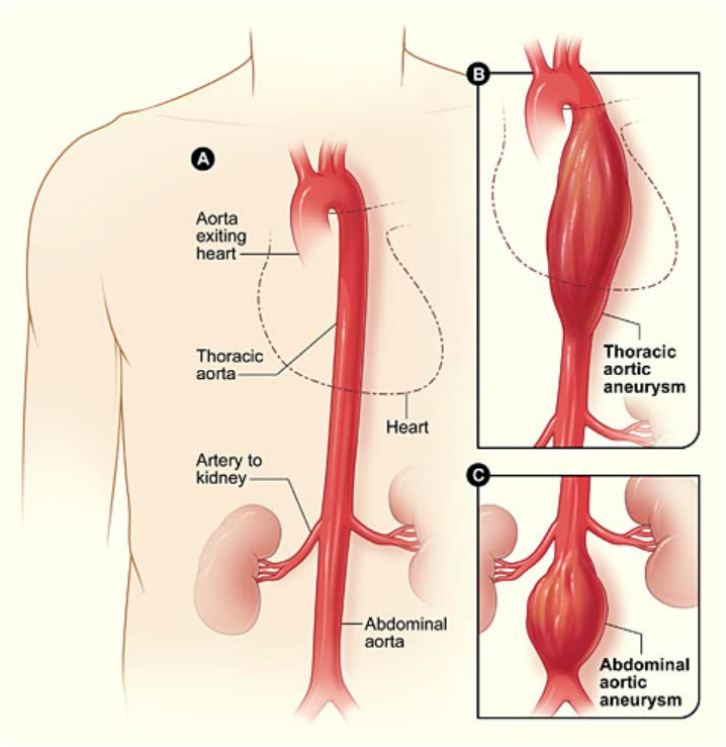
- Patients with pre-existing damage to native cardiac valve or prosthetic valve at increased risk
- Symptoms may include -isolated relapsing fever, chills, night sweats, weight loss, and hepatosplenomegaly
- Difficult to diagnose
  - Routine blood cultures negative
  - Vegetative lesions rarely identified 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



Aortic aneurysms. *Figure A shows the thoracic and abdominal sections of a normal aorta. Figure B shows a thoracic aortic aneurysm. The one in this figure is located behind the heart. Figure C shows an abdominal aortic aneurysm.*

Pediatric chronic Q fever infection

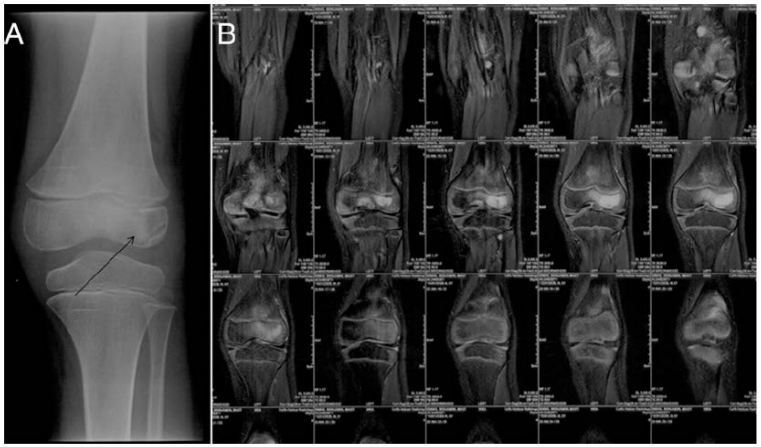


FIGURE 1
A, left knee x-ray demonstrating lytic lesion in the distal femur (black arrow). B, left knee MRI demonstrating T2 hyperintense lesion with sclerotic margins in the lateral distal femoral epiphysis.

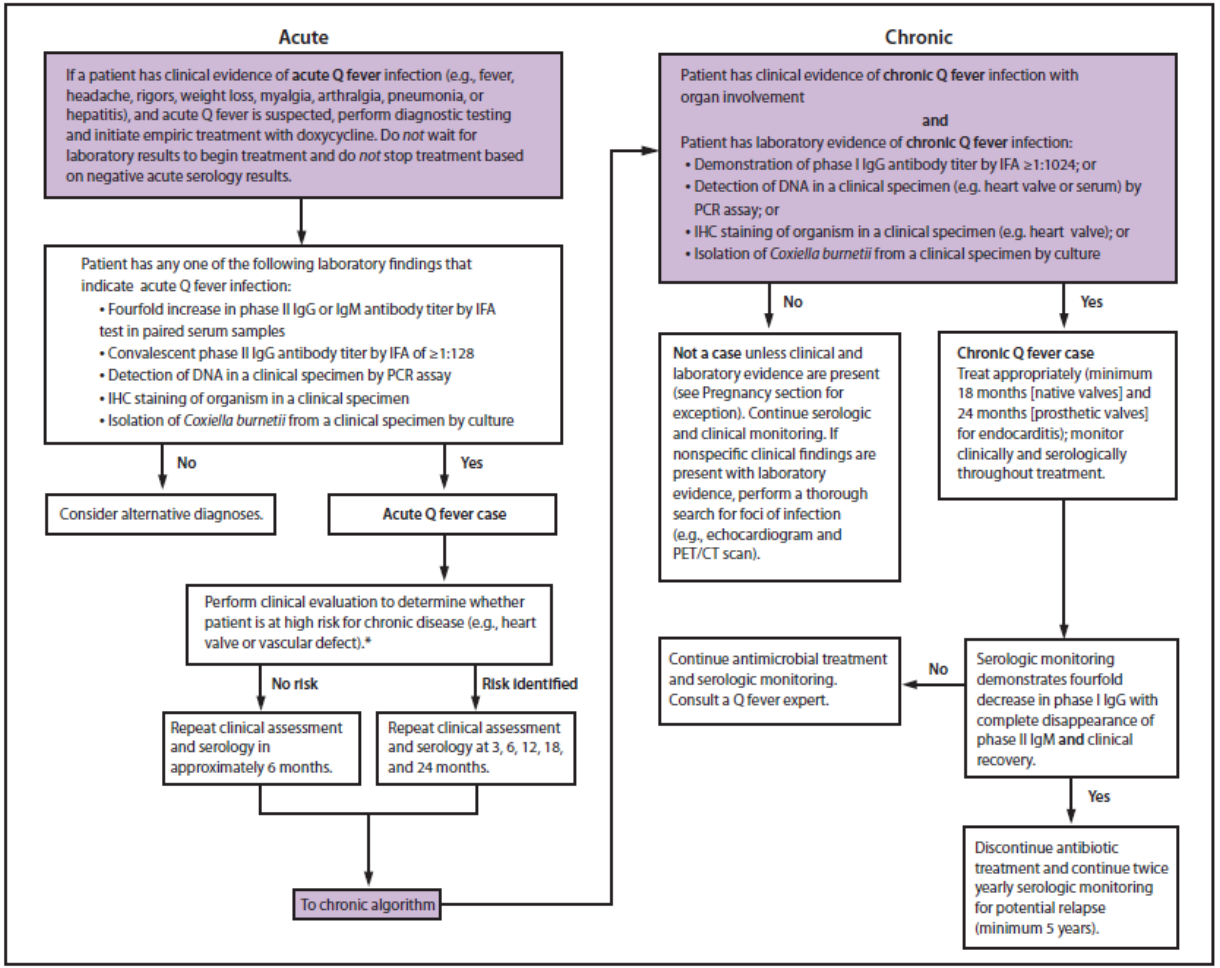
- Rarely reported
- Most frequently a chronic relapsing or multifocal osteomyelitis
  - Prolonged course with recurrent episodes affecting multiple bones

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
  - Hydroxycholorquine 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*



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

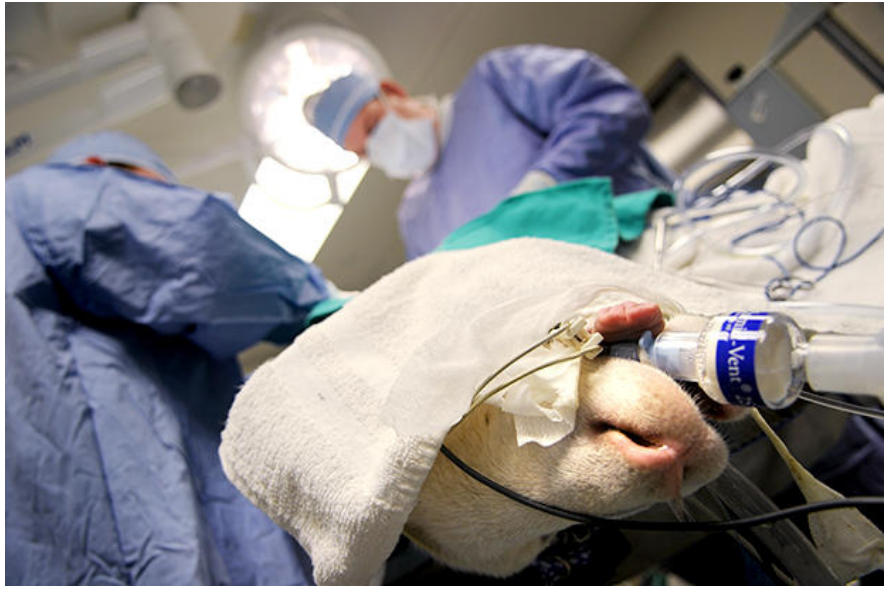
Military personnel are an emerging at-risk group.

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

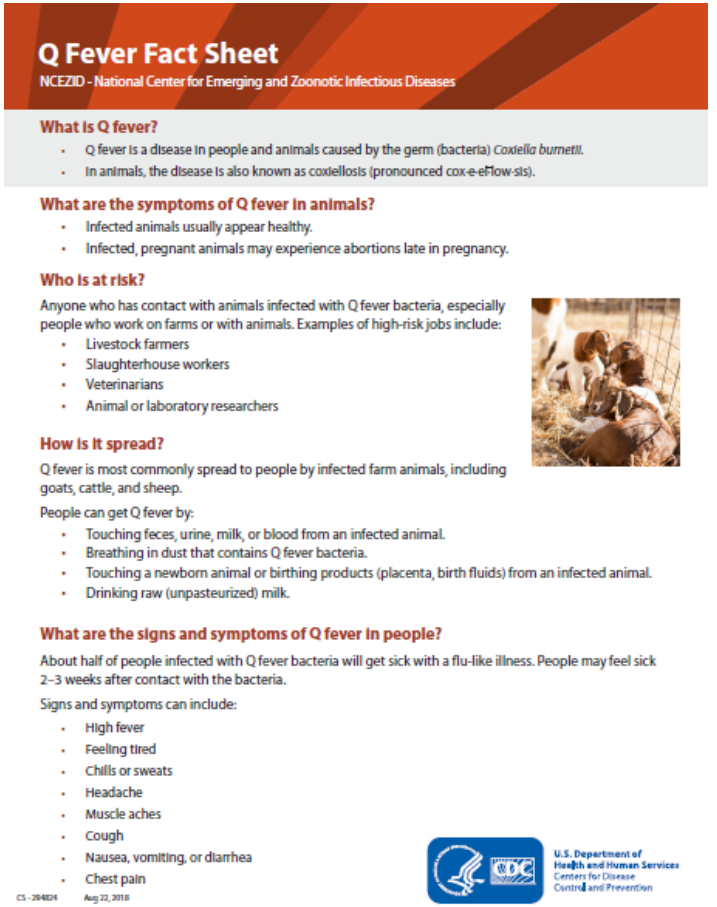
Potential control measures for workplaces with high exposure risk

- Educational training
- Medical surveillance
- Engineering controls
- Use of PPE
- Prophylaxis is not recommend



New Q fever factsheets

- English
- Spanish
- Arabic
- French
- Vietnamese
- Simplified Chinese



Q Fever Fact Sheet

NCEZID - National Center for Emerging and Zoonotic Infectious Diseases

What is Q fever?

- Q fever is a disease in people and animals caused by the germ (bacteria) *Coxiella burnetii*.
- In animals, the disease is also known as coxiellosis (pronounced cox-e-eFlow-sis).

What are the symptoms of Q fever in animals?

- Infected animals usually appear healthy.
- Infected, pregnant animals may experience abortions late in pregnancy.

Who is at risk?

Anyone who has contact with animals infected with Q fever bacteria, especially people who work on farms or with animals. Examples of high-risk jobs include:

- Livestock farmers
- Slaughterhouse workers
- Veterinarians
- Animal or laboratory researchers

How is it spread?

Q fever is most commonly spread to people by infected farm animals, including goats, cattle, and sheep.

People can get Q fever by:

- Touching feces, urine, milk, or blood from an infected animal.
- Breathing in dust that contains Q fever bacteria.
- Touching a newborn animal or birthing products (placenta, birth fluids) from an infected animal.
- Drinking raw (unpasteurized) milk.

What are the signs and symptoms of Q fever in people?

About half of people infected with Q fever bacteria will get sick with a flu-like illness. People may feel sick 2–3 weeks after contact with the bacteria.

Signs and symptoms can include:

- High fever
- Feeling tired
- Chills or sweats
- Headache
- Muscle aches
- Cough
- Nausea, vomiting, or diarrhea
- Chest pain

CS - 294824 Aug 22, 2018

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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 footware

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

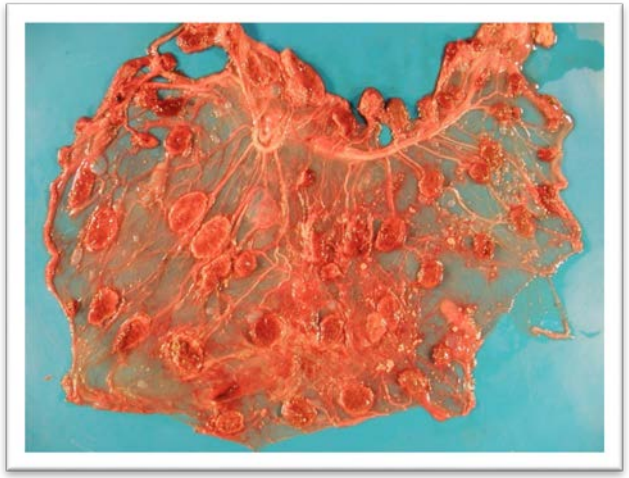


Photo credit: Dr. J. Arzt, PIADC and Center for Food Security and Public Health at Iowa State University, College of Veterinary Medicine

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.

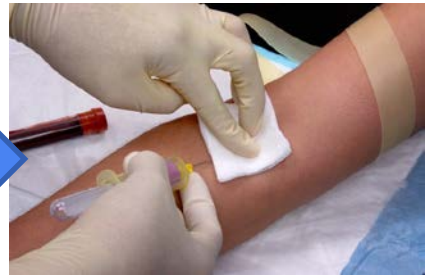
NNDSS
National Notifiable Diseases Surveillance System

Q fever surveillance in the United States

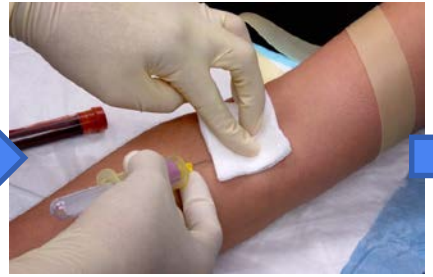
- National surveillance began in 1999 to better identify outbreaks related to bioterrorism.
  - No differentiation between acute and chronic cases.
- Chronic Q fever added to case definition in 2007.
- State and local health departments report cases of Q fever to CDC
  - National Notifiable Disease Surveillance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

Q fever Surveillance

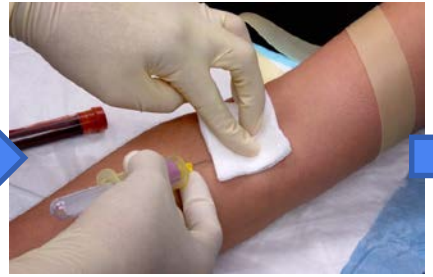
Q fever Surveillance

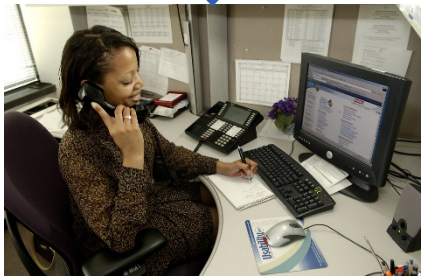


Q fever Surveillance

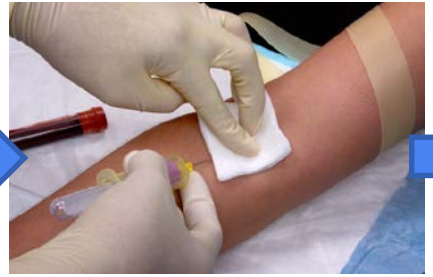


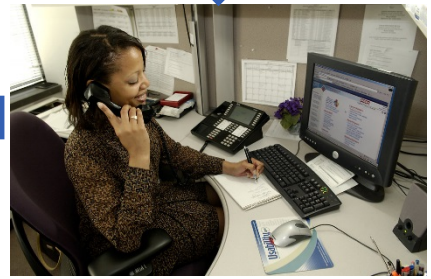
Q fever Surveillance





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 ≥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. Characteristics of Confirmed Chronic Q Fever Cases Among 686 Patients With Acute Q Fever

Patient no.	Sex	Age	Serology at 3 months IgG I	Serology at 3 months IgG II	Serology at 6 months IgG I	Serology at 6 months IgG II	Serology at 12 months IgG I	Serology at 12 months IgG II	PCR (Ct value)	Known clinical risk factor at time of diagnosis acute Q fever	Clinical signs at follow-up	Treatment
1	m	75	1:128	1:4096	1:8192	1:32768	1:2048	1:4096	At 6 months (35.1/undet)	Cardiac valve disease	Endocarditis	At 7 months
2	m	76	1:32	1:4096	1:128	1:1024	1:512	1:1024	At 21 months (29.8/29.6)	None	Infected aneurysm	At 21 months
3	m	70	1:32768	1:16384	1:32768	1:16384	1:4096	1:4096	At 12 months (29.2/29.9)	Cardiac valve disease	Endocarditis	At 1 month
4	m	54	1:1024	1:4096	1:1024	1:4096	1:4096	1:8192	At 12 months (33.9/34.2)	Vascular disease	Infected aneurysm	At 14 months
5	m	51	na	na	1:8192	1:32768	1:8192	1:8192	Negative	None	Persistent fever, nummular eczema	At 15 months
6	m	63	1:2048	1:8192	1:1024	1:4096	1:4096	1:16384	At 3 months (35.2/35.0)	Vascular disease	None	At 12 months
7	f	51	1:256	1:2048	1:8192	1:2048	1:8192	1:2048	At 6 months (36.4/undet)	None	None	No treatment
8	m	66	1:32768	1:65536	1:4096	1:16384	1:512	1:4096	Negative	Cardiac valve disease	Endocarditis	At 4 months
9	f	61	1:4096	1:65536	1:256	1:4096	1:64	1:2048	Negative	Cardiac valve disease	None	At 3 months
10	f	82	na	na	1:1024	1:4096	1:2048	1:16384	At 6 months (36.1/undet)	Unknown	Unknown	No treatment
11	m	73	1:256	1:2048	1:1024	1:4096	1:2048	1:16384	At 6 months (35.9/undet)	Unknown	Unknown	No treatment

NOTE. na, no serum sample available; undet, undetermined Ct value.

Table I 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.

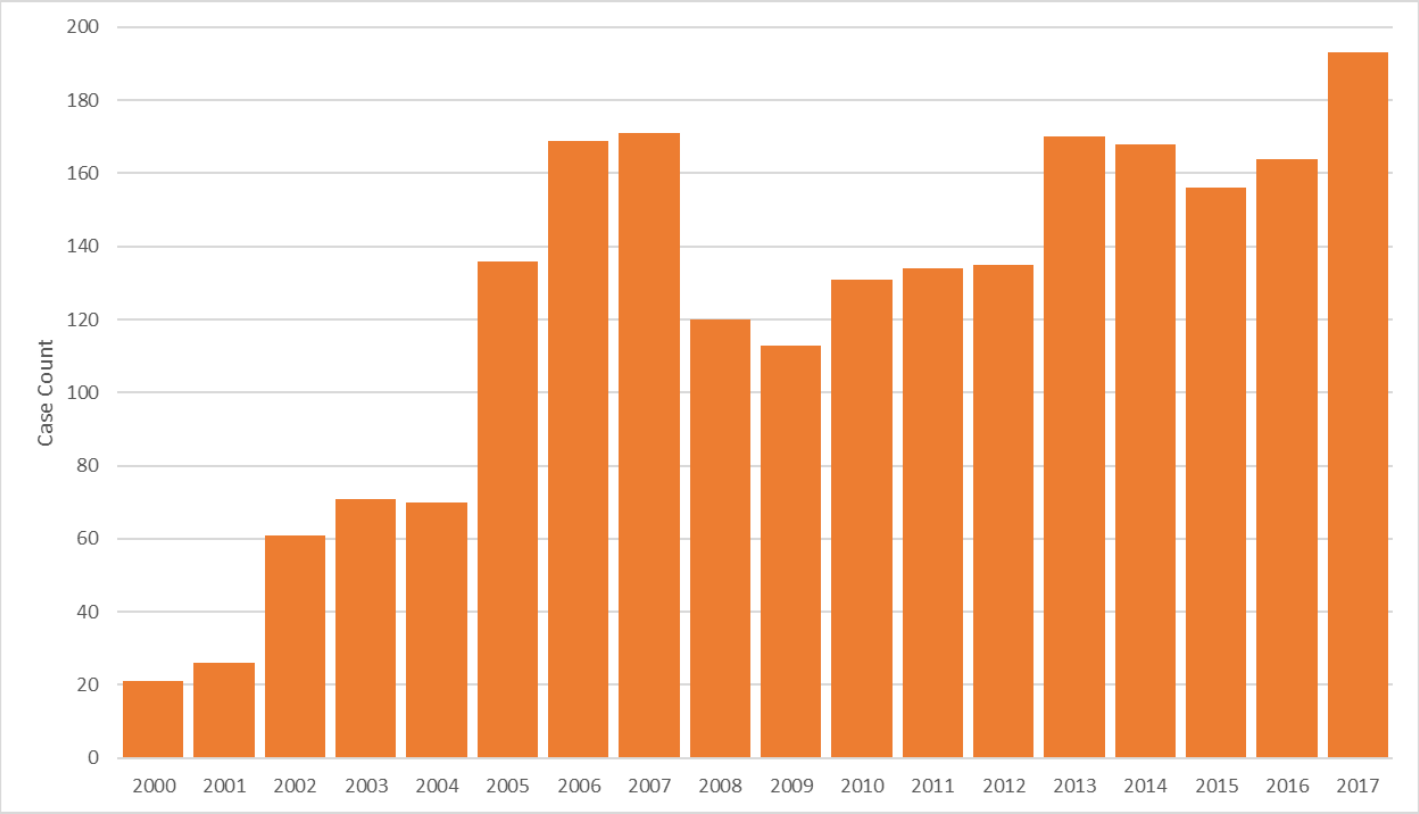
What does commercial Q testing in the United States show?

Table 1. Serology titers of specimens

		Phase I													
	Titer	<16	16	32	64	128	256	512	1,024	2,048	4,096	8,192	16,384	≥32,768	Total
Phase II	<16	53,898	145	64	38	17	10	3	1	1	1	0	0	0	54,178
	16	658	547	129	98	21	7	8	0	0	0	0	0	0	1,468
	32	390	424	270	135	40	8	5	1	0	0	0	0	0	1,273
	64	472	663	330	501	124	72	10	3	1	0	0	0	0	2,176
	128	183	295	243	344	258	124	28	9	3	0	0	0	0	1,487
	256	102	208	128	381	213	323	63	46	9	2	0	1	0	1,476
	512	34	18	21	51	75	91	109	51	16	5	1	0	0	472
	1,024	31	11	12	43	23	125	57	296	33	27	3	1	0	662
	2,048	23	4	4	9	16	20	24	51	97	45	12	2	0	307
	4,096	8	2	1	4	5	15	12	31	22	41	22	19	3	185
	8,192	7	0	1	3	3	5	8	17	10	17	20	32	17	140
	16,384	4	0	1	0	0	0	2	7	10	12	13	21	30	100
	≥32,768	2	0	0	1	1	0	2	5	5	5	11	21	129	182
	Total	55,812	2,317	1,204	1,608	796	800	331	518	207	155	82	97	179	64,106

Table 1 from Miller et al. (2018). Trends in Q fever serologic testing by immunofluorescence from four large reference laboratories in the United States, 2012–2016. Nature Scientific Reports, 8: 16670. https://www.nature.com/articles/s41598-018-34702-2

Number of annual Q fever cases 2000–2017

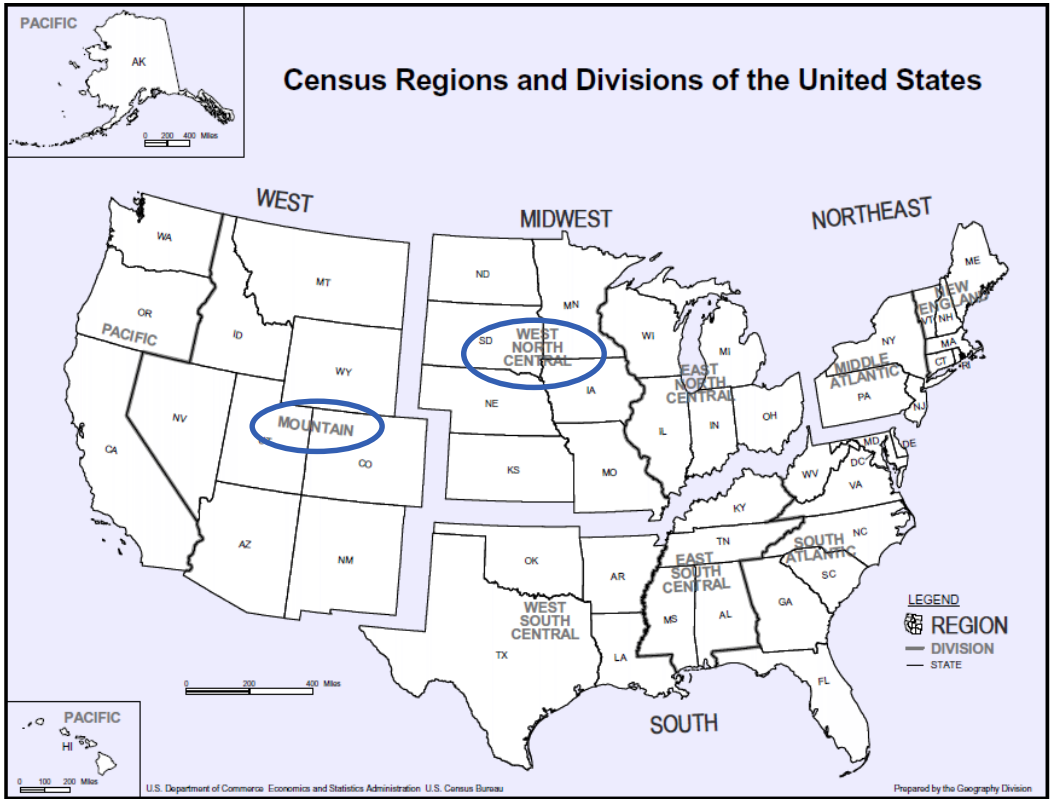


Q fever Surveillance Summary — United States, 2000–2012

- 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

Dahlgren, FS, McQuiston, JH, Massung, RF & Anderson, AD. (2014). Q fever in the United States: Summary of case reports from two national surveillance systems, 2000–2012. AJTMH: 92(2), 247–255.

Geographic divisions with highest incidence rates.

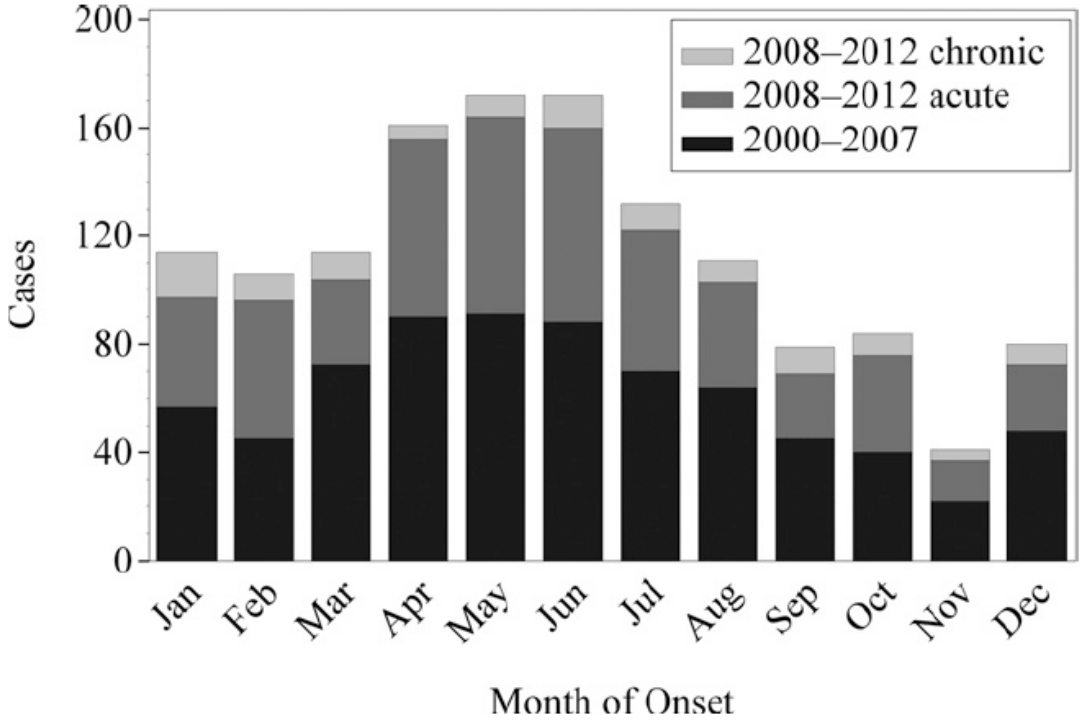


Occupations of Cases Reported to National Surveillance

- 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

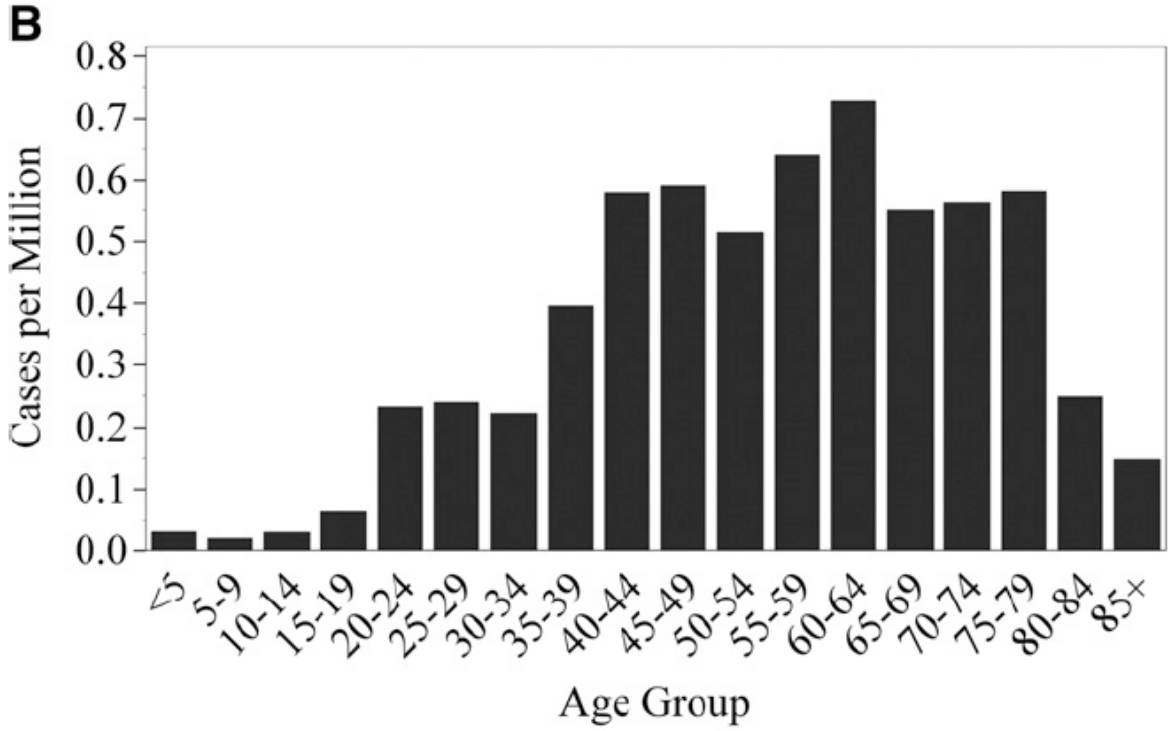
Dahlgren, FS, McQuiston, JH, Massung, RF & Anderson, AD. (2014). Q fever in the United States: Summary of case reports from two national surveillance systems, 2000–2012. AJTMH: 92(2), 247–255.

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



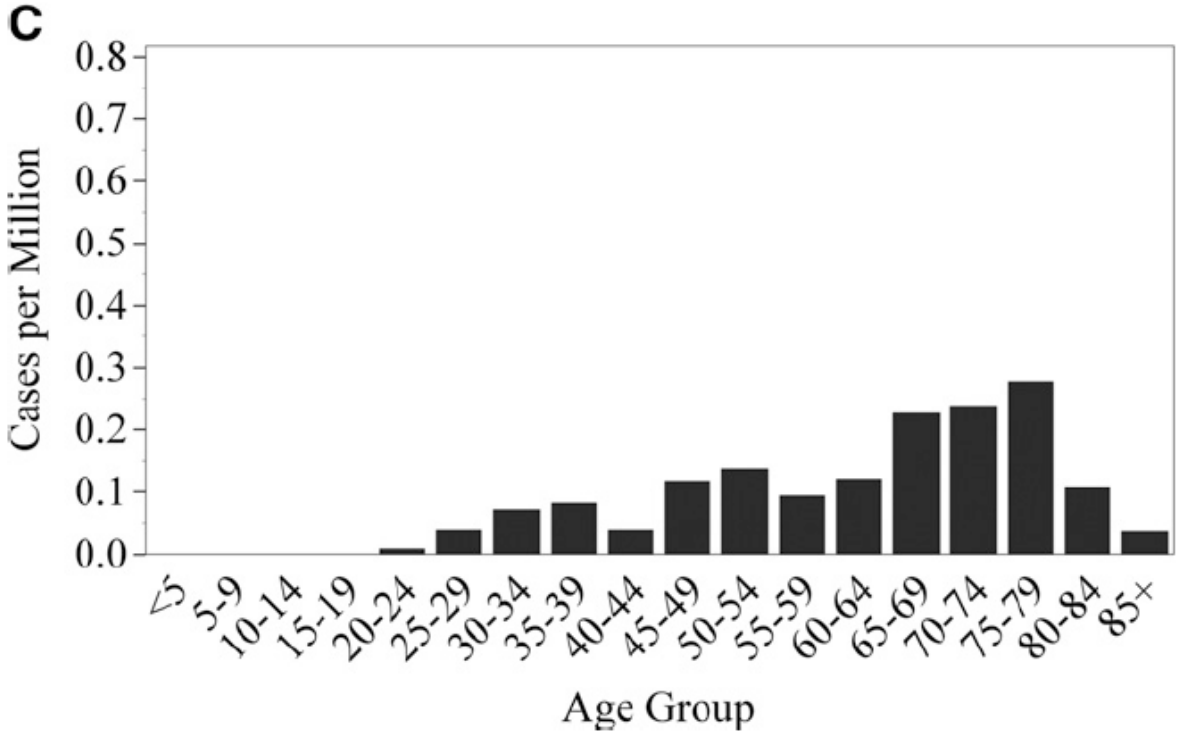
Dahlgren, FS, McQuiston, JH, Massung, RF & Anderson, AD. (2014). Q fever in the United States: Summary of case reports from two national surveillance systems, 2000–2012. AJTMH: 92(2), 247–255.

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



Dahlgren, FS, McQuiston, JH, Massung, RF & Anderson, AD. (2014). Q fever in the United States: Summary of case reports from two national surveillance systems, 2000–2012. AJTMH: 92(2), 247–255.

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



Dahlgren, FS, McQuiston, JH, Massung, RF & Anderson, AD. (2014). Q fever in the United States: Summary of case reports from two national surveillance systems, 2000–2012. AJTMH: 92(2), 247–255.

Resources

- National Association of State Public Health Veterinarians and National Assembly of State Animal Health Officials. Prevention and Control of *Coxiella burnetii* Infection among Humans and Animals: Guidance for a Coordinated Public Health and Animal Health Response, 2013. Available at: http://www.nasphv.org/Documents/Q_Fever_2013.pdf
- 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
- USDA. (2012). Evaluation of factors that would initiate or propagate epidemic coxiellosis in the U.S. domesticated goat population. USDA:APHIS:VS:Centers for Epidemiology and Animal Health. Fort Collins, CO. June 2013. 104 pages. Available at: https://www.aphis.usda.gov/animal_health/emergingissues/downloads/QFeverRiskAssessment_FINAL.pdf
- CDC Q Fever website: https://www.cdc.gov/qfever/index.html

Questions?

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