

# Bru and Q:

## A Review of Brucellosis and Q Fever: Two Zoonotic Diseases with Much in Common – and Some Surprising Differences

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## Human Brucellosis Overview:



- a.k.a. undulant fever, Malta fever, Mediterranean fever
- Bacterial disease (gram negative coccobacillus) with mammalian reservoirs that can infect humans
  - *Brucella melitensis* – sheep & goats
  - *Brucella abortus* – cattle
  - *Brucella canis* – dogs
  - *Brucella suis* – swine
  - *Brucella ceti* and *B. pinnipedialis* – sea critters

*B. melitensis* is considered to be the most virulent species to humans

## Brucellosis Symptoms in Humans:



- Undulating fever, often most severe at night (“night sweats” is a common complaint)
- Headache
- Fatigue (often extreme and prolonged) & weakness
- Myalgia & arthralgia
- GU involvement (orchitis, epididymitis)
- Fetal demise
- NVD, liver swelling, anorexia & weight loss
- Rarely, neuro and cardiac involvement

## Brucellosis Human Epi Info:



- Distribution is worldwide, particularly Mediterranean, Africa, Near- and Middle-East, South & Central America, Mexico
- Incubation period is variable and can be extensive (ranges from 5 days to 5 months, with 1-2 months being typical)
- Fatality rate is low (2%) and is usually associated with cardiac complications

## At-Risk Human Population for Brucellosis:



- Occupational: veterinarians, animal farmers & breeders, lab workers, dairy & slaughterhouse workers
- Avocational: animal hobbyists, hunters
- Diet: consumption of undercooked meats, unpasteurized dairy
- People with heart valve defects
- Human-to-human transmission is rare

Theoretical human-to-human transmissions are sexual, vertical and breastfeeding

# Human Brucellosis Testing/Case Definition



Case Ruling Table for Brucellosis:

Test or Condition	Presence of Compatible Sx	Absence of Sx/Sx unknown
Culture Positive	Confirmed	Rule-Out
4-fold Increase in Titers (same lab, specimens taken at least 2 weeks apart)	Confirmed	Rule-Out
PCR Positive	Probable	Rule-Out
Strongly positive single test (>160 by agglutination)	Probable	Rule-Out
Weakly positive single test (<160 by agglutination)	Rule-Out	Rule-Out
Other tests (ELISA, etc.) – in situations with strong clinical compatibility, try to get another test performed	Rule-Out	Rule-Out
Epi Link to confirmed human or animal case	Probable	Rule-Out

Positive tests for *Brucella* spp. in humans are reportable within 1 working day

## Human Brucellosis Treatment:



- Doxy/rifampin for at least 6 weeks
- Streptomycin or other abx for at least 6 weeks
- Relapses can occur even with Tx
- Special isolation precautions are not indicated (unless there are actively draining lesions)
- Prevention education, especially with at-risk populations – PPE for occupational exposures, don't eat unpasteurized dairy foods

## Q Fever Overview



- a.k.a. Query Fever
- Agent is a small, Rickettsia-like gram-negative bacterium, *Coxiella burnetii*. It can be persistent in the environment (airborne)
- Reservoir is animals, which can infect humans. Milk, urine, feces and especially products of birthing are vehicles for transmission. Tick-borne transmission is considered rare.

## Q Fever Symptoms in Humans



- Chills, fever, sweats (especially at night)
- Myalgia
- Headache
- Malaise, fatigue
- NVD
- Pneumonitis (rare)
- Liver & neuro Sx
- Endocarditis (chronic infection, rare)

## Q Fever Human Epi Info:



- Distribution: Worldwide (especially where livestock are)
- Incubation: 3-30 days with 2-3 weeks typical
- Fatality rate is 1% (usually assoc. w endocarditis)

# One Health Implications

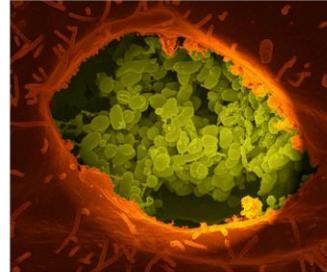


One Health relates to the intersection of human, animal, and environmental health. One Health is important because nearly 75% of newly emerging infectious disease agents are zoonotic diseases, meaning that these diseases can be transmitted from animals to people. We know that Q-fever and Brucellosis are both zoonotic diseases, and are designated as agents of bioterrorism. There is also a threat to international trade if animals are found to be infected.

## *C. burnetii* (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.

## Q Fever in Animals- Overview



- Arizona typically has reports of 0 to 1 animal cases reported each year
- Prevalence data in animals is limited
  - California is considered an endemic area
- Transmission is animal to animal

*Coxiella burnetii* can survive 7-10 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. Domestic livestock, sheep, cattle, and goats, are the most common reservoirs of Q fever.

The incubation period for animals is variable.

Affected animals are usually asymptomatic; when clinical disease occurs, reproductive failure is usually the only symptom seen. This 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. Lambings subsequent to *Coxiella* abortions have been found to be carried to term. However ewes can remain chronically infective and continue to shed organisms.

Organisms may be shed in milk, and feces for several days after the delivery of the baby.

## Q Fever in Animals



- Sheep, cattle, goats
  - Usually asymptomatic, inapparent
  - Reproductive failure
    - Abortions, stillbirths
    - Retained placenta
    - Infertility
    - Weak newborns
    - Low birth weights
    - Mastitis in dairy cattle
  - Carrier state



## Q Fever in Animals

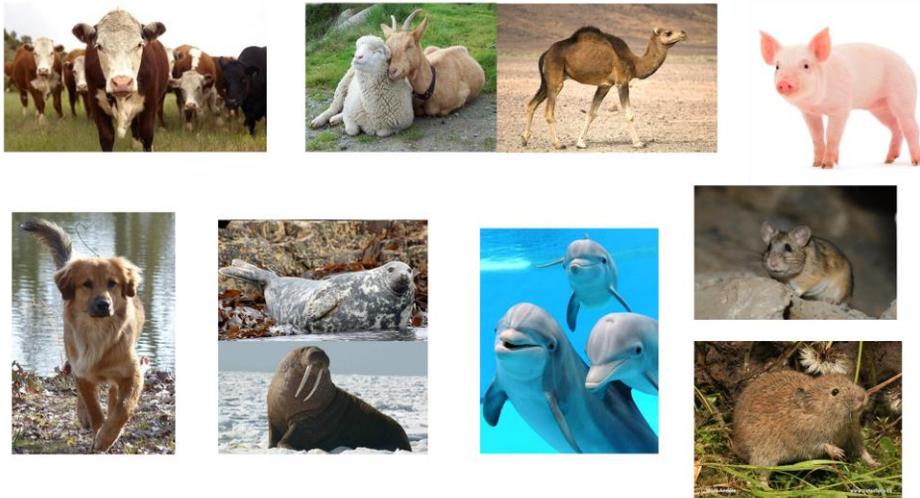


- Other animal species
  - Dogs, cats, horses, pigs, camels, buffalo, pigeons, other fowl
  - Asymptomatic
  - Reproductive failure
- Laboratory Animals
  - Rats, rabbits, guinea pigs, hamsters
  - Varies from asymptomatic to fever, granulomas, or death
- Even ixodid (hard) ticks



Dogs, cats, rabbits, horses, pigs, camels, buffalo, rodents, pigeons, geese and other fowl may also carry *C. burnetii*. Antibodies to the organism have been found in a variety of other animal species as well. Dogs and cats may be infected by a tick bite, consumption of placentas or milk from infected ruminants or by the aerosol route. Q fever infection in parturient dogs may lead to early death of pups. Human Q fever cases were described in Nova Scotia after contact with parturient cats. Twelve patients developed a febrile illness two weeks after playing poker in a room where a cat had given birth to kittens. All the infected persons had handled the cat or its litter, and specific antibodies were demonstrated in the cat serum. Infections can occur in a range of domestic and wild animals but are considered uncommon in US

## Host Animals for *Brucella* spp.



*B. abortus* Cattle, *B. melitensis* Goats, sheep, camels, *B. suis* Pigs, *B. canis* Dogs, *B. ovis* Sheep, goats, *B. neotomae* Wood rats, *B. pinnipediae* Pinnipeds (seals, sea lions, walruses), *B. ceti* Cetaceans (dolphins, porpoises, whales), *B. microti* Common vole. The primary reservoirs are goats, cattle, sheep, pigs and camels although animals such as elk, caribou, bison, deer and wild and domestic canine animals may be infected.

(Javelinas cannot carry brucella but there is concern for rabies, distemper for pets, and salmonella. There is a feral swine problem with brucellosis in other states.

*B. canis* is VERY rare in cats- would not be concerned but there is a report from 1993. Other animals such as horses and deer can also be affected.

# Brucellosis in Animals- Overview



- Arizona has been brucellosis-free since 1998
- *B. abortus* RB-51 strain vaccine available for cattle and bison
- *B. melitensis* Rev-1 vaccine available for sheep and goats
- Attenuated-live
- Symptoms of illness typically include abortions, birth of weak offspring, and occasionally enlarged, arthritic joints



Vaccination must be performed by a USDA-accredited veterinarian

## Transmission from Animals to People (Q Fever)



- Inhalation of dust/droplets (birthing fluids, urine, feces, milk, wind-borne)
- Direct contact
- Fomites
- Ingestion
- Arthropods (ticks)
- Person-to-person (rare)
  - Transplacental (congenital)
  - Blood transfusions
  - Bone marrow transplants
  - Intradermal inoculation
  - Possibly sexually transmitted

Transmission to humans occurs through (a) direct contact of infected tissue or body fluids with broken skin or conjunctivae, (b) inhalation of infected aerosols, or (c) ingestion of raw infected meat or unpasteurized dairy products.

Guidance for exposures to RB51 differs from that of exposure to *Brucella* species.

Low risk of exposure for pet owners but there is increased risk for veterinary staff and dog breeders, since they may be exposed to blood, tissues, and fluids associated with the birthing process, as well as laboratory staff. Currently, there are no serological tests to detect antibodies to *Brucella canis*.

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Q fever can be transmitted via a variety of routes. Domestic ruminants represent the most frequent source of human *C. burnetii* infection. However, pets, (i.e., cats, dogs and rabbits) have also been involved as sources of urban outbreaks. Aerosolization is the primary mode of transmission in humans. 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, wool/hair, during necropsies or assisting deliveries. Due to the persistence of the organism in the environment, dried infective material can contaminate dust or soil, which can be carried considerable distances by wind and has been documented to travel downwind up to  $\frac{1}{2}$  mile or more. This has resulted in cases of patients without any evident contact with animals.

Fomites (i.e., newborn animals, wool, bedding, clothing) can also be contaminated by such materials and serve as a source of the transmission. Organisms shed in urine and feces of infected animals can also serve as a source of water, dust, soil or fomite contamination. Water may be contaminated and act as a vehicle for dissemination. 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. Person-to-person transmission is extremely rare, with the exception of transplacental transmission resulting in congenital infections. Transmission from blood transfusions, bone marrow transplants, intradermal inoculations have been reported. Demonstrated in semen and testicular swelling.

## Transmission from Animals to People (Brucellosis)



- Inhalation
- Consumption (undercooked meat, unpasteurized/raw dairy products)
- Direct contact/exposure through skin wounds or mucous membranes to infected animals or animal excretions (fetuses, birthing fluids, etc.)
- Person-to-person (rare): breastfeeding, sexual, transplantation or blood transfusions

## Role of Public Health and Animal Health Partners



- People (local health departments)
  - Brucellosis and Q-fever: providers must submit a report within one working day after a case or suspect case is diagnosed, treated, or detected
- Animals (Arizona Department of Agriculture)
  - Brucellosis (in cattle, pigs, goats, and sheep) and Q-fever within 4 hours
- Communication and education is key!

Both Brucellosis and Q-fever are reportable in both humans and animals. The key is- we are probably missing many animal cases that are not reported! Communication is KEY to preventing human illnesses once a positive animal is detected.

## Q-fever Investigation



In a 9-year old child in Yavapai County in 2016 had to be hospitalized. Found out that the family owned goats

# Sampling goats to test for *Coxiella burnetii*



# Gathered Risk Factor Information



## Q-fever Prevention and Control



- Pasteurization
- Personal protective equipment
- Eradication not practical
  - Too many reservoirs
  - Constant exposure
  - Stability of agent in environment
- Improve animal husbandry practices



Q-fever: Pasteurization of milk from cows, sheep, and goats is important in stopping the spread of Q fever by contaminated milk sources. Vaccines have been developed for both animals and humans, but are not commercially available in the United States. Persons previously exposed to *C. burnetii* should not receive the vaccine because severe reactions are possible. Practical control is difficult because of environmental stability and infectivity for wild animals, arthropods, and humans. For livestock, control includes good animal husbandry, vaccination, screening, and culling. Education is an important part of prevention and control of Q fever. It should focus on potential sources of infection and ways to reduce environmental contamination from infected placental membranes and aborted materials. When possible, lambing should take place indoors and in separate facilities for parturition. Placentas, aborted materials and fetal tissues should be disposed of appropriately. Birth products should be incinerated and lambing areas treated with Lysol, bleach, or hydrogen peroxide. Vaccination (human and animal): Not available in U.S.

## At-Risk Human Population for Q-Fever (Same as Brucellosis):



- Occupational: veterinarians, animal farmers & breeders, lab workers, dairy & slaughterhouse workers
- Avocational: animal hobbyists, hunters
- Diet: consumption of undercooked meats, unpasteurized dairy
- People with heart valve defects
- Human-to-human transmission is rare

## Human Q-Fever Testing/Case Definition I



- First, determine whether case is acute or chronic (Sx lasting more than 6 months).
- Testing can seem complicated: Two antigenic preparations are tested: Phase I is the antigen *sensu-stricta* and is mostly used to guide CHRONIC case rulings, Phase II is a biochemically altered version of the antigen and is mostly used to interpret ACUTE cases.

Theoretical human-to-human transmissions are sexual, vertical and breastfeeding. Investigators should be a bit wary of IgM+ only as false positives can/do occur. Reports of low titer “+” Q-fever (e.g. 1:16 / 1:32 / etc.) are very common. These low titers are NOT worth spending time investigating as they never pan-out.

# Human Q-Fever Testing/Case Definition II



Test	Acute Sx verified	Chronic Sx verified	Asx or Sx unknown
Culture: Positive	Confirmed	Confirmed	Rule out
PCR: Positive	Confirmed	Confirmed	Rule out
IFA: Phase I IgG $\geq$ 1:800	Probable**	Confirmed	Rule out
IFA: Phase I IgG 1:128-1:800	Probable**	Probable	Rule out
IFA: 4-fold change in Phase II IgG ABs*	Confirmed	--	Rule out
IFA: Phase II IgG $\geq$ 1:128	Probable	--	Rule out
ELISA or Agglutination: IgG +/- IgM elevated	Probable	Rule out	Rule out
IHC: Positive	Confirmed	Rule out	Rule out
Epi link to lab confirmed case	Confirmed	--	Rule out

\*ideal timing is preliminary test within the first week of Sx, follow-up test done 3-6 weeks later

\*\*This ruling is based on an interpretation of the case definition – a consult with AZDHS-VBZD may be in order

Theoretical human-to-human transmissions are sexual, vertical and breastfeeding. Investigators should be a bit wary of IgM+ only as false positives can/do occur. Reports of low titer “+” Q-fever (e.g. 1:16 / 1:32 / etc.) are very common. These low titers are NOT worth spending time investigating as they never pan-out.

## Human Q-Fever Treatment:



- Acute cases: Doxy x14 days or other Abx (Cotrimaxazole) where Doxy is contraindicated
- Chronic cases: Doxy/Hydroxychloroquine x18-24 months with monitoring for Sx & serology at 3, 6, 12, 18 & 24 months
- Use standard precautions
- Prevention education, especially with at-risk populations – PPE for occupational exposures, don't eat unpasteurized dairy foods

# 10-year Brucellosis Trend in Maricopa County (Humans):



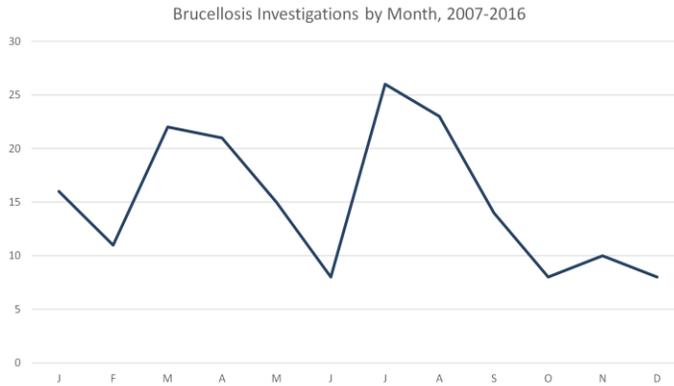
Brucellosis Investigations and Cases per Year, 2007-2016



Over the 10-year period, we investigated 182 reports of suspected brucellosis. Of these, 29 confirmed or probable cases were found. That averages about 3 cases per year out of 18 investigations. About 16% of reports investigated yield an actual case.

So far in 2017 we are seeing more cases of brucellosis than usual (5+ cases already). Our increase typically reflects a probable increase south of the border.

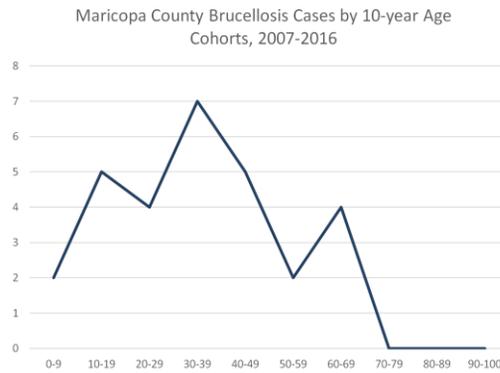
# Monthly Trend in Human Brucellosis Investigations, Maricopa County, 2007-2016



# Human Brucellosis Cases in Maricopa County Basic Demographics, 2007-2016



Cases by Age Cohorts:	
0-9	2
10-19	5
20-29	4
30-39	7
40-49	5
50-59	2
60-69	4
70-79	0
80-89	0
90-100	0
median age = 33	



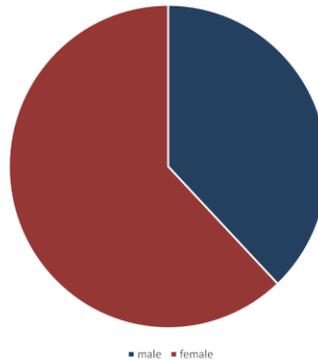
There were no Brucella-associated deaths from 2007-2016

# Human Brucellosis Cases in Maricopa County Basic Demographics, 2007-2016



Cases by sex:	
female	18
male	11

Human Brucellosis Cases in Maricopa County, 2007-2016, by Sex



■ male ■ female

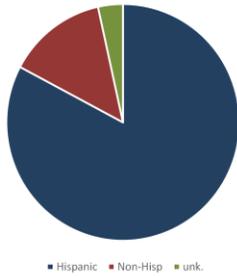
# Human Brucellosis Cases in Maricopa County Basic Demographics, 2007-2016



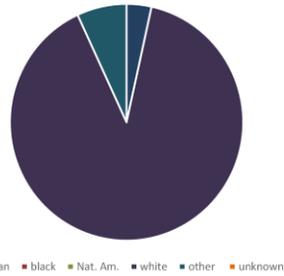
Cases by Ethnicity:	
Hispanic	24
non-Hisp	4
unk.	1

Cases by Race:		
Asian	1 white	26
black	0 other	2
Nat. Am.	0 unknown	0

Human Brucellosis Cases in Maricopa County, 2007-2016, by Ethnicity



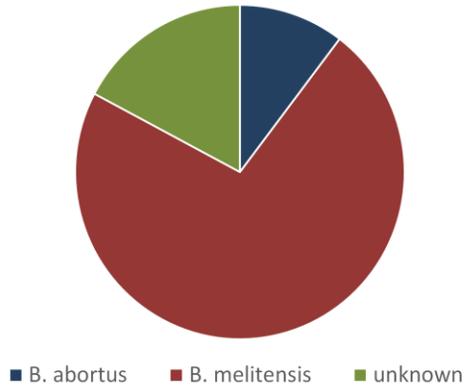
Human Brucellosis Cases in Maricopa County, 2007-2016, by Race



# Human Brucellosis Cases in Maricopa County: 10-Year Overview



Brucella species breakdown, 2007-2016



# Human Brucellosis Cases in Maricopa County: Sources of Exposure (10-Year Summary)

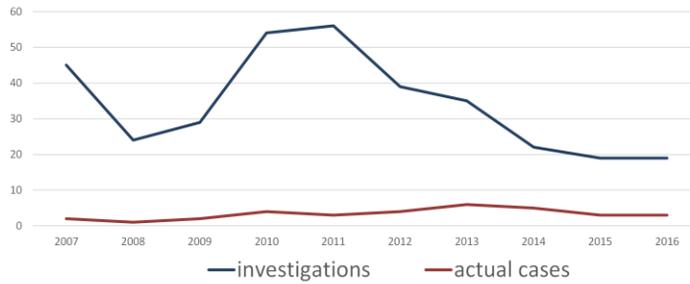


Risk/Exposure Among Brucellosis cases, 2007-2016*			
		number	% of all cases
travel to Mexico		15	51.72414
travel to Caribbean		1	3.448276
travel to India		1	3.448276
travel to Middle-East		2	6.896552
travel to Guatemala		1	3.448276
unpasteurized dairy		19	65.51724
contact w animals		4	13.7931
lab exposure		1	3.448276
*some pt's have multiple exposures			

# 10-year Q Fever Trend in Maricopa County (Humans):



Q Fever Investigations and Actual Cases, 2007-2016



Over the 10-year period, we investigated 342 reports of suspected Q-fever. Of these, 33 confirmed or probable cases were found. That averages about 3 cases per year out of 34 investigations. About 10% of reports investigated yielded an actual case.

# Monthly Q Fever Trend in Maricopa County (Humans):



Q Fever Investigations by Month, 2007-2016



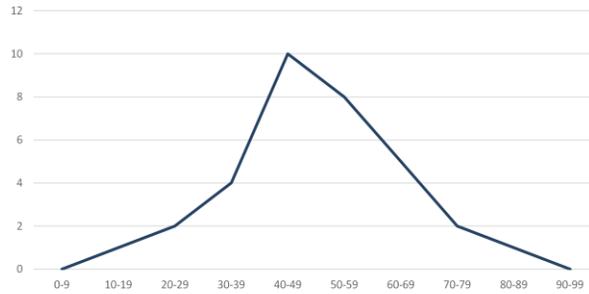
# Human Demographic Trends, Q Fever in Maricopa County, 2007-2016



Maricopa County Q Fever Cases by 10-year Age Cohorts, 2007-2016

Cases by age cohorts:

0-9	0
10-19	1
20-29	2
30-39	4
40-49	10
50-59	8
60-69	5
70-79	2
80-89	1
90-99	0



Cases by outcome:

died*	2
survived	31
	33

\*deaths were in 56, 86 YO Pts

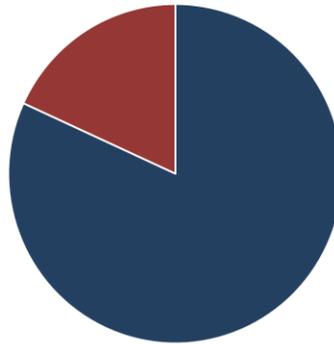
Median Pt age is 49 Y

# Human Demographic Trends, Q Fever in Maricopa County, 2007-2016



Cases by sex:	
Female	6
Male	27

Human Q Fever Cases in Maricopa County, 2007-2016 by Sex



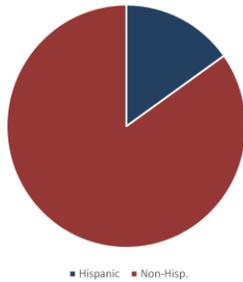
■ male ■ female

# Human Demographic Trends, Q Fever in Maricopa County, 2007-2016



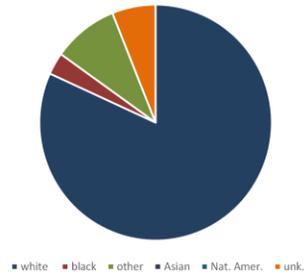
Cases by ethnicity:	
Hispanic	5
Non-Hisp.	28

Human Q Fever Cases in Maricopa County, 2007-2016 by Ethnicity



Cases by Race:			
Asian	0	white	27
black	1	other	3
Nat. Am.	0	unk.	2

Human Q Fever Cases in Maricopa County, 2007-2016 by Race



# Human Demographic Trends, Q Fever in Maricopa County, 2007-2016



## Cases by Exposure:

### occupational (n=2, 6% of cases):

vet	1
vet's spouse	1

### animal contact (n=20, 56% of cases):

sheep	1
goats	5
cattle	4
dogs	2
cats	6
horses	2

### food Hx (n=3, 9% of cases):

raw dairy	3
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### travel (n=6, 18% of cases):

Mexico	2
C. America	2
Mid-East	1
Africa	1

Unknown Exposure: 11 (33% of cases)

## Conclusions



- Awareness for people with occupational/avocational exposures to animals
- Avoid unpasteurized dairy
- Prompt Dx and Tx
- Steady case counts for both diseases over 10 years
- Human Brucellosis cases tend to skew towards younger, female and Hispanic populations as compared with Q Fever cases, which are predominantly male, older and non-Hispanic
- Both diseases are potential bioterrorism agents
  
- QUESTIONS?