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Ovine and Caprine Brucellosis:
Brucella melitensis
Undulant Fever,
Malta Fever,
Mediterranean Fever,
Contagious Abortion

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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 ovine and caprine brucellosis and its epidemiology. We will also talk about the history of the disease, how it is transmitted, species that it affects (including humans), and clinical and necropsy signs observed. Finally, we will address prevention and control measures, as well as actions to take if ovine and caprine brucellosis is suspected.

[Photo: (Top) Goat. Source: Wikimedia-commons; (Bottom) Sheep. Source: flickr-creative-commons]

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THE ORGANISM

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The Organism

- *Brucella melitensis*
  - Gram negative coccobacillus
  - Facultative intracellular pathogen
- Three biovars
  - All cause disease in small ruminants
  - Geographic distribution varies
- Can persist in environment

In sheep and goats, brucellosis is mainly caused by *Brucella melitensis*, a Gram–negative coccobacillus or short rod. This organism is a facultative intracellular pathogen. *B. melitensis* contains three biovars (biovars 1, 2 and 3). All three biovars cause disease in small ruminants, but their geographic distribution varies. *Brucella abortus* and *Brucella suis* infections also occur occasionally in small ruminants, but clinical disease seems to be rare. Genetic and immunological evidence suggests that all members of the genus *Brucella* are closely related, and some microbiologists have proposed that this genus be reclassified into a single species (*B. melitensis*), which contains many biovars. This proposal is controversial, and both taxonomic systems are currently in use. *Brucella* spp. can persist in the environment invariably depending on temperature, pH, and humidity.

[Photo: Micrograph of *Brucella* organisms. *Brucella* spp. are gram-negative in their staining morphology. *Brucella* spp. are poorly staining, small gram-negative coccobacilli (0.5-0.7 x 0.6-1.5 µm), and are seen mostly as single cells and appearing like "fine sand". Source: CDC Public Health Image Library #1901]

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The Many Names of Brucellosis

Human Disease	Animal Disease
• Malta Fever	• Bang's Disease
• Undulant Fever	• Enzootic Abortion
• Mediterranean Fever	• Epizootic Abortion
• Rock Fever of Gibraltar	• Slinking of Calves
• Gastric Fever	• Ram Epididymitis
	• Contagious Abortion

Due to its illustrious history, brucellosis has many different names. The disease is commonly known as undulant or Malta fever in humans and Bang's disease in animals.

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EPIDEMIOLOGY

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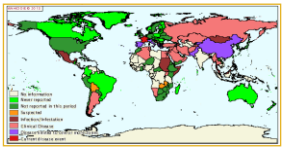
Geographic Distribution

- Mediterranean region, Middle East
- Central America
- Sporadic cases in other countries



B. melitensis is particularly common in the Mediterranean. It also occurs in the Middle East, Central Asia, around the Arabian Gulf, and in some countries of Central America. This organism has been reported from Africa and India, but it does not seem to be endemic in northern Europe, North America (except Mexico), Southeast Asia, Australia, or New Zealand. Biovar 3 is the predominant biovar in the Mediterranean countries and the Middle East, and biovar 1 predominates in Central America. Sporadic cases or incursions are occasionally reported in *B. melitensis* - free countries. In the U.S., cases have mainly been reported in imported goats and rarely in cattle.

[Photo: Map of disease distribution of *Brucella melitensis* in animals worldwide, Jan-June 2012. Source: World Organization for Animal Health WAHID at http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/Diseasedistributionmap]

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Species Affected

- Mainly sheep and goats
- Occasionally
  - Cattle, camels, dogs
- Rarely
  - Horses, pigs
- Humans are very susceptible

Most species of *Brucella* are primarily associated with certain hosts; however, infections can also occur in other species, particularly when they are kept in close contact. *Brucella melitensis* mainly infects sheep and goats. Most breeds of goats are readily infected, but sheep breeds vary greatly in susceptibility. *B. melitensis* infections are also been reported occasionally in cattle, camels and dogs, and rarely in horses and pigs. Infections in sheep and goats can spill over into wild ruminants; *B. melitensis* infections have been reported in alpine ibex in Italy and chamois in the French Alps. However, there is no evidence that these animals serve as reservoir hosts for domesticated sheep and goats.

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Human Populations at Risk

- Occupational disease
  - Laboratory workers
  - Farmers
  - Veterinarians
- Consumers of unpasteurized dairy products
- Vaccine-exposed

B. melitensis is highly pathogenic for humans; this organism is considered to be the most severe human pathogen in the genus. Occupational exposure is seen in laboratory workers, farmers, veterinarians and others who contact infected animals or tissues. People who do not work with animals or tissues usually become infected by ingesting unpasteurized dairy products. The Rev-1 *B. melitensis* vaccine is also pathogenic for humans and must be handled with caution to avoid accidental injection or contamination of mucous membranes or abraded skin.

[Photo: (Top) Bottles of raw milk. Source: Kyle McDaniel/Wisconsin State Journal; (Bottom) Goat cheese. Source: wikimeida.commons.org]

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HISTORY

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History of Brucellosis

- Sir William Burnett (1779-1861)
  - Physician General to the British Navy
  - Differentiated among the various fevers affecting soldiers

The island of Malta was given to the Knights of the Order of St. John in 1530, and contagious fevers were noted from that time well into the 19th century. During the 17th and 18th centuries there were numerous reports of undulant fevers from all over the Mediterranean and most were given local names (Mediterranean fever, Rock fever of Gibraltar, Cyprus fever, Danube fever). Sir William Burnett was a physician to the British Navy in 1810 and was the first person to differentiate between the various fevers affecting seamen in the Mediterranean. It is thought that Malta became such an important center for the study of undulant fever because many British troops were sent there to recuperate following the Crimean War (1853-1856), along with skillful medical doctors utilizing clinical thermometers to monitor the disease progression.

[Photo: Sir William Burnett. Source: U.S. National Library of Medicine – Images from the History of Medicine]

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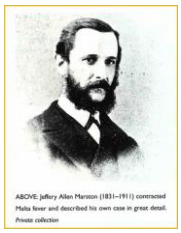
History of Brucellosis



- Jeffery Allen Marston
  - British Army surgeon
  - Contracted Malta fever
  - Described his own case in great detail

J.A. Marston was an army surgeon (British) who, after contracting the Malta fever, wrote the first detailed account of the disease (his own illness). He was afflicted with an irregular fever for 30 to 90 days, gastrointestinal symptoms, and muscle and joint pains.

[Photo: Jeffery Allen Marson. Source: The Wellcome Trust Illustrated History of Tropical Diseases]

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History of Brucellosis

- Sir David Bruce (1855-1931)
  - British Army physician and microbiologist
  - Discovered *Micrococcus melitensis*

The microorganism responsible for Malta fever was discovered by a British Army physician, Sir David Bruce, on July 9, 1887, which he called *Micrococcus melitensis*. It was isolated from the spleen of a British soldier who had died of the disease. He also identified that the organism grew best at higher temperatures and speculated that this accounted for the increased frequency of cases in hot summer months. He later established goats as the main reservoir for infection by identifying the organism in their blood, urine, and milk. This discovery helped explain the epidemiology of the disease. For example, officers were three times more likely to become ill because they drank more milk than private soldiers, and large numbers of cases were found in hospitals where milk was widely distributed.

[Photo: Sir David Bruce. Source: The Wellcome Trust Illustrated History of Tropical Diseases]

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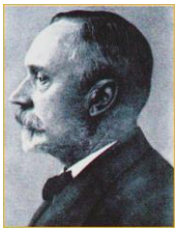
History of Brucellosis



- Bernhard Bang (1848-1932)
  - Danish physician and veterinarian
  - Discovered *Bacterium abortus* could infect cattle, horses, sheep, and goats

A Danish physician and veterinarian, Bernhard Bang discovered *Bacterium abortus* in 1897 while investigating contagious abortion that had been affecting cattle in Denmark for over a century. He also discovered the organism affected horses, sheep, and goats. Thus the disease became known as "Bang's disease".

[Photo: Bernhard Bang. Source: The Wellcome Trust Illustrated History of Tropical Diseases]

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History of Brucellosis

- Alice Evans
  - American bacteriologist credited with linking the organisms in the 1920s
  - Discovered similar morphology and pathology between:
    - Bang's *Bacterium abortus*
    - Bruce's *Micrococcus melitensis*
- *Brucella* nomenclature
  - Credited to Sir David Bruce

The connection between animals and humans was discovered by Alice Evans, an American bacteriologist in the 1920s. The morphology and pathology of the organism was very similar between Bang's *Bacterium abortus* and Bruce's *Micrococcus melitensis*. The name of Sir David Bruce has been carried on in today's nomenclature of the organisms.

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TRANSMISSION

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Transmission in Humans

- Contact with infected animal tissues
  - Placenta, fetus, fetal fluids, vaginal discharges
- Consumption of unpasteurized dairy products
- Laboratory-acquired
- Accidental injection
  - Rev-1 *B. melitensis* vaccine

Brucellosis can be acquired by contact with infected animal tissues or fluids, including the placenta, fetus, fetal fluids, and vaginal discharges. People who do not work with animals or tissues usually become infected by ingesting unpasteurized dairy products. Brucellosis is one of the most easily acquired laboratory infections.
Accidental injection of the Rev-1 *B. melitensis* vaccine can also cause disease in humans.

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Transmission in Sheep and Goats

- Small ruminants infectious after abortion or full-term parturition
  - Contact or ingestion
    - Placenta, fetus, fetal fluids, vaginal discharges
  - Variable shedding
- Milk
- Venereal (semen)
- *In utero*

In animals, *B. melitensis* is usually transmitted by contact with the placenta, fetus, fetal fluids and vaginal discharges from infected animals. Small ruminants are infectious after either abortion or full-term parturition. Goats usually shed *B. melitensis* in vaginal discharges for at least 2 to 3 months, but shedding usually ends within three weeks in sheep. This organism can also be found in the milk and semen; shedding in milk and semen can be prolonged or lifelong, particularly in goats. However, transmission during breeding seems to be uncommon during natural mating. Kids and lambs that nurse from infected dams may shed *B. melitensis* in the feces. In utero infections also occur.

[Photo: Goat and kid. Source: LT Hunter/wikimedia-commons-org]

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Transmission in Other Animals

- Contact with infected sheep, goats
- Shedding in milk
  - Cattle
  - Camels
- Fomites

Cattle and other species can be infected with *B. melitensis* after contact with infected sheep and goats. It has not been established whether cattle can maintain this species indefinitely in the absence of contact with small ruminants. Cattle with infected udders can shed *B. melitensis* in the milk for months or years. Camels also shed this organism in milk. *B. melitensis* can be spread on fomites, and could be disseminated mechanically by carnivores that carry away infected material.

Photo: Cow and goat. Source: Tiffany Wisser/The Ecolutionist]

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DISEASE IN HUMANS

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Disease in Humans

- May be asymptomatic
- If symptomatic:
  - Disease is variable
  - Often begins as acute febrile illness with influenza-like signs
- Spontaneous recovery possible
- Disease may wax and wane

Some *Brucella* infections are asymptomatic in humans. In symptomatic cases, the disease is extremely variable and the clinical signs may appear insidiously or abruptly. Typically, brucellosis begins as an acute febrile illness with nonspecific flu-like signs such as fever, headache, malaise, back pain, myalgia and generalized aches. Drenching sweats can occur, particularly at night. Some patients recover spontaneously, while others develop persistent symptoms that typically wax and wane.

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Treatment and Prognosis in Humans

- Possible complications
  - Arthritis, spondylitis, chronic fatigue, epididymo-orchitis
  - Neurologic signs
- Treatment with antibiotics
  - Relapses possible
- Low mortality
  - 2 to 5% (untreated cases)
  - Death from endocarditis, meningitis

Occasionally seen complications include arthritis, spondylitis, chronic fatigue, and epididymo-orchitis. Neurologic signs (including personality changes, meningitis, uveitis and optic neuritis), anemia, internal abscesses, nephritis, endocarditis and dermatitis can also occur. Other organs and tissues can also be affected, resulting in a wide variety of syndromes. Treatment is with antibiotics; however, relapses can be seen months after the initial symptoms, even in successfully treated cases. The mortality rate is low; in untreated persons, estimates of the case fatality rate vary from less than 2% to 5%. Deaths are usually caused by endocarditis or meningitis.

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DISEASE IN ANIMALS

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Clinical Signs: Sheep and Goats

- Mainly reproductive
  - Abortion, stillbirth, weak offspring
  - Reduced milk yield
  - Acute orchitis and epididymitis
  - Infertility
- Arthritis
- May be asymptomatic

The predominant symptoms in naturally infected sheep and goats are abortions, stillbirths and the birth of weak offspring. Animals that abort may retain the placenta. Sheep and goats usually abort only once, but reinvasion of the uterus and shedding of organisms can occur during subsequent pregnancies. Some infected animals carry the pregnancy to term, but shed the organism. Milk yield is significantly reduced in animals that abort, as well as in animals whose udder becomes infected after a normal birth. However, clinical signs of mastitis are uncommon. Acute orchitis and epididymitis can occur in males, and may result in infertility. Arthritis is seen occasionally in both sexes. Many non-pregnant sheep and goats remain asymptomatic.

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Clinical Signs: Other Animals

- Cattle
  - Abortion
- Camels
  - Abortion, orchitis, epididymitis
- Dogs
  - Often asymptomatic
  - Abortion, orchitis, epididymitis

B. melitensis has also been associated with abortions in cattle, and abortions, orchitis and epididymitis in camels. In wild chamois, this organism has been linked to epididymo-orchitis, polyarthritis, blindness and neurological signs, but abortion was not reported. In dogs, infection with *B. melitensis* is often asymptomatic, and rapid elimination of this organism has been reported. However, abortion, orchitis and epididymitis, and other symptoms of canine brucellosis can also occur.

[Photos: (Top) Cow. Source: Renee Dewell/CFSPH; (Bottom) Dog. Source: Danelle Bickett-Weddle/CFSPH]

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Post Mortem Lesions

- Granulomatous inflammatory lesions
  - Reproductive tract
  - Udder
  - Supramammary lymph nodes
  - Joints and synovial membranes
- Necrotizing orchitis, epididymitis
- Autolyzed fetus
- Placentitis

At necropsy, granulomatous inflammatory lesions may be present in the reproductive tract, udder, supramammary lymph nodes, other lymphoid tissues, and sometimes in the joints and synovial membranes. Necrotizing orchitis, epididymitis, seminal vesiculitis and prostatitis have been reported. The fetus may be autolyzed, normal or have an excess of bloodstained fluid in the body cavities and an enlarged spleen and liver. Placentitis, with edema and/or necrosis of the cotyledons and a thickened and leathery intercotyledonary region can be seen. These lesions are not pathognomonic for brucellosis.

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Morbidity and Mortality

- Importance varies by region
  - Influenced by husbandry practices
  - Susceptibility of breeds
- High abortion rate in naïve herds
- Milk yield decreased
- Fertility impairment in males
  - May be permanent
- Death is rare

B. melitensis is a significant problem in small ruminants, particularly in developing nations where infections can be widespread. The relative importance of *B. melitensis* for sheep and goats varies with the geographic region, and can be influenced by husbandry practices and the susceptibility of sheep breeds in the region. Management practices and environmental conditions significantly influence the spread of infection. Lambing or kidding in dark, crowded enclosures favors the spread of the organism, while open air parturition in a dry environment results in decreased transmission. The abortion rate is high when *B. melitensis* enters a previously unexposed and unvaccinated flock or herd, but much lower in flocks where this disease is enzootic. Ruminants usually abort only during the gestation when they are first infected. Inflammatory changes in infected mammary glands usually reduce milk yield by a minimum of 10%. Fertility in males can be permanently impaired. Deaths are rare except in the fetus.

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Differential Diagnosis

- Consider brucellosis when:
  - Abortion and stillbirth occur without concurrent illness
- Diseases to consider:
  - Chlamydiosis
  - Coxiellosis
  - *Brucella ovis*

Brucellosis should be considered in flocks and herds when abortions and stillbirths occur without concurrent illness. Other diseases causing abortion in small ruminants, particularly chlamydiosis and coxiellosis, should be considered. *B. ovis* can also cause epididymitis and orchitis in rams.

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Laboratory Diagnosis

- Microscopic exam
- Serology
  - Screening
  - Brucella antigen test, complement fixation, ELISA
- Culture and identification
  - Phage typing, biological and serological characteristics
- PCR

Microscopic examination of semen or smears stained with the Stamp's modification of the Ziehl-Neelsen method can be useful for a presumptive diagnosis. Serology can be used for a presumptive diagnosis of brucellosis, or to screen flocks. Serological tests are not completely specific and cannot always distinguish reactions due to *B. melitensis* from cross-reactions to other bacteria. The most commonly used serological tests in small ruminants are the buffered *Brucella* antigen tests (the card and rose bengal (RB) plate agglutination tests) and the complement fixation test. Indirect or competitive enzyme-linked immunosorbent assays (ELISAs) are also used. A definitive diagnosis can be made if *B. melitensis* is cultured from an animal. *Brucella* spp. can be isolated on a variety of plain media, or selective media such as Farrell's medium or Thayer-Martin's modified medium. *B. melitensis* can be identified to the species and biovar level by phage typing and cultural, biochemical and serological characteristics. Genetic techniques can also be used for biotyping. The vaccine strain (*B. melitensis* strain Rev.1) can be distinguished from field strains by its growth characteristics and sensitivity to antibiotics and other additives. Polymerase chain reaction (PCR) techniques and other genetic techniques (PCR restriction fragment length polymorphism or Southern blotting) are available in some laboratories.

[Photo: Microbiology test tubes. Source: Danelle Bickett-Weddle/CFSPH]

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Collecting Samples

- Milk samples
- Vaginal swabs
- Aborted fetuses
- Placenta
- At necropsy
  - Spleen, mammary and genital lymph nodes, udder, uterus

Milk samples and vaginal swabs are particularly useful for diagnosis in live sheep and goats. *B. melitensis* can also be cultured from aborted fetuses (stomach contents, spleen and lung) or the placenta. The spleen, mammary and genital lymph nodes, udder and late pregnant or early post-parturient uterus are the most reliable samples to collect at necropsy. This organism can also be cultured from semen, the testis or epididymis, and arthritis or hygroma fluids.

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

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PREVENTION AND CONTROL

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Recommended Actions

- Notification of authorities
  - Federal Area Veterinarian in Charge (AVIC)
    http://www.aphis.usda.gov/animal_health/area_offices/
  - State Veterinarian
    http://www.aphis.usda.gov/emergency_response/downloads/nahems/fad.pdf

B. melitensis is considered exotic to the U.S. State and/or federal authorities should be consulted immediately for specific guidance if brucellosis is suspected.

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Prevention and Control

- May be introduced into herd by:
  - Infected animal
  - Semen
- Test and slaughter
  - Include shepherd dogs
- Infection control
  - Cleaning, disinfection, good hygiene

B. melitensis is most likely to be introduced into a herd in an infected animal. Semen could also be a source of infection. This organism can be eradicated from a herd by test and slaughter procedures, or by depopulation. In areas where *B. melitensis* is not endemic, infected herds are usually quarantined and the animals are euthanized. Because dogs can be infected, some countries require that shepherd dogs also be euthanized, or treated with antibiotics and castrated, when flocks are depopulated. Any area exposed to infected animals and their discharges should be thoroughly cleaned and disinfected. Infections in other species are generally prevented by controlling *B. melitensis* in sheep and goats.

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Prevention and Control

- *B. melitensis* Rev1 vaccine
  - Used in endemic areas
  - Attenuated live vaccine
  - Can cause abortions
  - Interferes with serological tests
    - Minimized by conjunctival administration in lambs and kids
  - Not licensed in U.S.

The Rev1-*B. melitensis* vaccine is used to control this disease in infected areas. Rev1 can cause abortions in pregnant animals. This vaccine also interferes with serological tests, particularly when it is injected subcutaneously, but conjunctival administration to lambs and kids between the ages of 3 and 6 months minimizes this problem. The vaccine is administered to three- to six-month-old females or in much lower doses to older females. This vaccine is not currently licensed in the United States.

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Prevention and Control

- Education about risk of transmission
  - Veterinarians, farmers, animal husbandry clubs, laboratory workers
- Wear proper attire if dealing with infected animals/tissues
  - Gloves, masks, goggles

Educate those at greatest risk about the routes of transmission of brucellosis. Those who have the greatest occupational exposure are people who come into contact with infected animals or tissues from infected animals. These include veterinarians, farmers, members of animal husbandry clubs, and laboratory workers. Properly protecting yourself, if you are an "at risk" individual, by wearing gloves, masks, goggles, and coveralls to prevent exposure to tissues and body secretions of infected animals can help.

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Prevention and Control

- Readily killed by most disinfectants
  - Hypochlorite
  - 70% ethanol
  - Isopropanol
  - Iodophores
  - Phenolics
  - Formaldehyde/glutaraldehyde
- Quaternary ammonium compounds not recommended

Brucella species are readily killed by most commonly available disinfectants including hypochlorite solutions, 70% ethanol, isopropanol, iodophores, phenolic disinfectants, formaldehyde, glutaraldehyde and xylene; however, organic matter and low temperatures decrease the efficacy of disinfectants. Alkyl quaternary ammonium compounds are not recommended. Autoclaving [moist heat of 121°C (250°F) for at least 15 minutes] can be used to destroy *Brucella* species on contaminated equipment.

[Photo: Disinfection bottles. Source: Dani Ausen/CFSPH]

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Additional Resources

- Center for Food Security and Public Health
  - www.cfsph.iastate.edu
- CDC Brucellosis
  - http://www.cdc.gov/ncidod/dbmd/diseaseinfo/brucellosis_g.htm

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Acknowledgments

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Authors: Kerry Leedom Larson, DVM, MPH, PhD, DACVPM; Anna Rovid Spickler, DVM, PhD; Sarah Viera, MPH
Reviewer: Glenda Dvorak, DVM, MPH, DACVPM

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