Zoonosis Update

Brucellosis

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Brucellosis is one of the most common zoonotic diseases in the world and, as such, poses a major threat to human health and animal agriculture. In the United States, however, concentrated animal disease control programs, occupational safety practices, and food safety efforts have diminished the relative impact of brucellosis over the last half century. At its most basic level, brucellosis in humans is dependent on the presence of *Brucella* spp among other animals with which people have direct or indirect contact. As with many classic zoonotic diseases, the role of veterinarians is critical for the detection and continued prevention and control of brucellosis. This role remains vital, as a recent study[1] again drew attention to the difficulty among human health-care professionals in recognizing and diagnosing brucellosis in humans in nonendemic areas.

Background

Brucellosis is a bacterial infection that systemically affects a wide variety of mammalian species, including humans. Brucellosis occurs worldwide, both endemically and enzootically to varying degrees, particularly in the Middle East.[2] Brucellosis appears to be an ancient disease; organisms associated with carbonized cheese and with bony lesions on skeletal remains in the ruins of Pompeii are consistent with *Brucella* spp and brucellosis, respectively.[3] In the late 1800s, *Brucella* organisms were identified as the cause of Malta fever; *Brucella melitensis* and *Brucella abortus* were subsequently isolated in the late 1890s. The relationship between contagious bovine brucellosis and human brucellosis was confirmed by Meyer and Shaw in 1920, and the earliest culture-confirmed human cases in the United States were described in the early 20th century.[4]

Etiologic Agent

Brucellosis is caused by a gram-negative coccobacillus. Six major species have been classically characterized: *B abortus*, *B melitensis*, *Brucella suis*, *Brucella canis*, *Brucella ovis*, and *Brucella neotomae*. In the last few decades, the taxonomic classification of *Brucella* spp has undergone debate, with some scientists proposing that all 6 *Brucella* spp should be classified as *B melitensis* on the basis of results of DNA-DNA hybridization, and the former species should be reclassified as biovars.[5] However, on the basis of host specificity, phenotypic characteristics, varying virulence, and increasingly available genotyping data,[6,7] the classic taxonomic scheme for the 6 *Brucella* spp and 17 existing biovars was ultimately reapproved in 2003.[8] In recent years, apparently new *Brucella* spp have been isolated from marine species, resulting in the proposal of 2 new species, *Brucella ceti* and *Brucella pinnipedialis*.[9,10] Additional new or seemingly novel species have also been described more recently,[11,12] which will ensure ongoing updates in the area of *Brucella* taxonomy for the near future.

Abbreviation

S-LPS	Smooth lipopolysaccharide

Brucella spp have a strong host preference, which is evident in their ability to establish chronic infection in individuals and maintain transmission and infection in populations of specific animal species. For *B abortus*, the host preference is cattle; for *B melitensis*, sheep and goats; for *B suis*, swine; for *B canis*, dogs; for *B ovis*, sheep; and for *B neotomae*, rodents (desert rat). *Brucella suis* has the widest host range, with established host-pathogen relationships in reindeer[13] and hares,[14] in addition to swine. However, almost all *Brucella* spp can infect mammalian species other than their preferred host; for example, both *B melitensis* and *B suis* are capable of colonizing bovine udders and therefore contaminating cows' milk.[15–17]

As a component of their identification, *Brucella* spp are also classified on the basis of the presence or absence of S-LPS; the presence of S-LPS appears to be associated with virulence. The commonly identified human pathogens *B abortus, B melitensis,* and *B suis* are characterized as smooth because S-LPS is present in their outer membrane. The remaining species (*B canis*, *B ovis*, and *B neotomae*) are characterized as rough strains, given that they express little or no S-LPS and cause less severe or no disease in humans.[18]

Molecular characterization has identified a great degree of homology among the brucellae.[6,19] Common genetic fingerprinting methods such as pulsed-field gel electrophoresis and multilocus sequence typing analyses have revealed little variability among isolates of a given species. However, multilocus sequence typing has been useful in identifying the relationship among various species and among biovars within species, and in general, the findings support the classification of *Brucella* into the 6

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known species, with at least 1 new species representing the newer marine strains of *Brucella*.[20] Multiple-locus variable-number tandem repeat analysis appears more effective at discriminating between different species and strains and shows promise for differentiation of strains associated with a local outbreak or investigation.[21] Multiple-locus variable-number tandem repeat analysis was recently used to differentiate isolates in 2 unrelated laboratory-acquired cases of brucellosis, when the laboratory workers had been exposed to more than 1 *Brucella* spp isolate.[22]

Mode of Transmission

Brucella organisms are present in the reproductive tissues and products of parturition at extremely high concentrations; placental samples from brucellosis-induced abortions have been quantified at 10^{10} organisms/g.[23] *Brucella* organisms also concentrate in the udders of animals that produce milk used for human consumption. Organisms can be found in meat, albeit at lower concentrations, and meat contamination is rarely a public health risk when meat products are properly handled and cooked. *Brucella* spp have a markedly low infectious dose for humans, estimated at 10 to 100 organisms[24]; as a result, *Brucella* organisms can be transmitted to humans through direct contact with infected tissue via breaks in skin, ingestion of contaminated tissues or milk products, and inhalation or mucosal exposure to aerosolized bacteria. Other routes, including in utero transmission,[25,26] person-to-person transmission,[27,28] and tissue transplantation–associated transmission,[29] have been identified or suggested but are much less common.

Brucellosis can develop after accidental injection with live *Brucella* vaccines[30,31] and is thus an occupational hazard for veterinarians. In addition, brucellosis is one of the most commonly acquired bacterial laboratory infections worldwide, in part because of its low infectious dose and ease of aerosolization, which is exacerbated by outdated laboratory practices such as plate sniffing.[22,32–35]

Among nonhuman animals, the predominant route of exposure for smooth strains of *Brucella* is through ingestion or inhalation of organisms that are present in fetal fluids or other birth products; herds are typically exposed following the introduction of an infected animal that subsequently gives birth or aborts a fetus, whereupon pasture or water become contaminated by these excretions. Transient disease (eg, abortions) can also develop following administration of a live *Brucella* vaccine, particularly the *B abortus* vaccine strain 19. Among dogs and sheep, transmission of rough strains of *Brucella* may be more common via the venereal route, although supporting data are limited. Brucellae are fairly hardy; organisms have been recovered from fetal and manure samples that remained in a cool environment for longer than 2 months. However, exposure to sunlight kills the organism within a few hours,[36] and the organism is susceptible to many common disinfectants.[37]

Epidemiology

The epidemiology of brucellosis among humans reflects the epidemiology among populations of other animals. To protect public health and mitigate the economic effect on the cattle industry, the USDA initiated a national brucellosis control program in 1934.[38] In 1954, this became a congressionally funded comprehensive state-federal effort to eradicate brucellosis from cattle, an effort that continues today.[39] In 1957, an estimated 13% of 1.8 million US cattle herds were infected with *Brucella* spp.[38] Since that time, the effectiveness of surveillance and control measures instituted in the national eradication campaign has led to a substantial decline in the number of affected US cattle herds. The national eradication program has made great progress, continuing diligently toward the ultimate goal of final eradication and declaration of all states as free of brucellosis.[40] As of February 2008, the program had achieved class-free status in all 50 states, Puerto Rico, and the US Virgin Islands. Supplemented by food safety improvements, particularly the pasteurization of dairy products, the decrease in brucellosis in cattle resulted in a dramatic decline in brucellosis in humans, from a peak of > 6,000 cases/y to approximately 100 to 150 cases/y during the past century.[41]

Brucellosis caused by *B suis* in swine was first described in the early 1900s in the United States.[4] Subsequent to implemented control measures among cattle, *B suis*–associated brucellosis among abattoir workers became more common in the 1960s and 1970s and was the leading cause of brucellosis in humans during this period.[42] Expansion of the national control program to swine herds in 1974 led to a substantial decrease in domestic swine brucellosis and again to decreased illness among humans. Currently, brucellosis in domestic swine and swine-associated brucellosis in humans in the United States are predominantly associated with exposure to infected feral swine.

Control of brucellosis among domestic animals in the United States faces continued pressure from the presence of brucellosis in US wildlife and also in domestic livestock (especially cattle and goats) across the southern border in Mexico. In the United States, brucellosis has become established in several wildlife populations, including among bison and elk in the Greater Yellowstone Area (*B abortus*),[43,44] feral swine in the southeastern United States (*B suis*[45] and *B abortus*[46]), and caribou in Alaska (*B suis*).[47] In Mexico, eradication programs among cattle populations have made substantial progress in controlling brucellosis, almost exclusively for brucellosis attributable to *B abortus*. Control of brucellosis among domestic goat herds (*B melitensis* infection) has proven more challenging; as reported in 1999, 93% of studied human cases in Mexico were the result of infection with *B melitensis* of caprine origin.[48] Therefore, brucellosis in humans in the United States can result from direct or indirect exposure to these infected animals or animal products.

Among dogs, the urine of males and vaginal secretions of females are the main sources of infection via the venereal, oral, nasal, or conjunctival routes.[49,50] The greatest impact of brucellosis is evident in breeding facilities, where chronic infections can become established and have considerable effect on breeding success. Data derived from molecular analysis of *B canis* strains associated with outbreaks suggest that *B canis*

is spread through interstate dog trade.[51] Unlike other rough strains, *B canis* is capable of causing human illness; however, *B canis*–associated illness is of decreased severity and frequency, compared with illness caused by the smooth *Brucella* strains. Limited data are available to quantify the zoonotic risk of *B canis* among humans; it has been estimated that as many as 1% of human brucellosis cases are attributable to *B canis*.[52] Individual sporadic, severe human infections have been reported,[53,54] but few US seroepidemiologic studies[55,56] have been reported in the literature. Consensus among experts remains, however, that human *B canis* infections are almost certainly under-recognized because of the insidious course of disease, a low index of suspicion among clinicians, and limited diagnostic tools.[52,57]

Brucellosis among marine mammals has been detected only in the last decade and a half, predominantly through serologic or microbiologic methods.[58] A wide variety of marine mammals can be affected, although the clinical implications of *Brucella* infections among marine mammals are still being investigated. Two main *Brucella* spp (as yet awaiting formal taxonomic classification) have been proposed: *B ceti* (affecting the larger sea mammals such as whales, dolphins, and porpoises) and *B pinnipedialis* (affecting seals, sea lions, and walruses).[10] There are currently only a few reports of human illness caused by the marine *Brucella* spp, but these describe severe disease such as spinal osteomyelitis and neurobrucellosis.[59–61]

Following an initial rapid decline, reported human brucellosis case counts have been relatively stable at approximately 100 to 150 reported cases/y during the last 2 decades (**Figure 1**). The brucellosis case definition for public health surveillance in the United States includes laboratory, clinical, and epidemiologic components (**Appendix**).[62] During 2006, 121 cases were reported to the CDC through the National Notifiable Diseases Surveillance System.[63] Reported cases most frequently involve adult males; for many cases, race or ethnicity is not reported, but when available, data indicate that affected individuals are predominantly white Hispanic persons. Half (50%) of the reported brucellosis cases in 2006 were from California, Texas, and Illinois. A recent study[64] of states bordering Mexico revealed that brucellosis case rates in the counties with borders adjacent to Mexico were twice the rates of nonadjacent counties and 8 times as high as the case rates from the remainder of the United States. Evaluations of brucellosis surveillance have suggested that surveillance data are incomplete.[41,65,66] Thus, the incidence of brucellosis in the United States is likely underestimated.

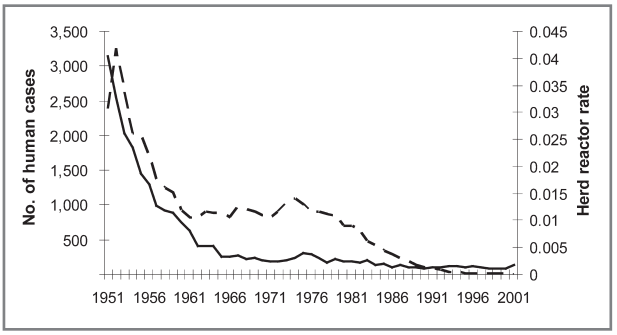

Figure 1—Annual numbers of reported human brucellosis cases* (solid line) and cattle herd reactors rates† (dashed line), 1951 through 2001, United States. *Number of cases reported to the National Notifiable Diseases Surveillance System.[62] †Percentage of cattle herds with an identified serologic reactor for brucellosis, as reported by USDA, APHIS, Veterinary Services, Brucellosis Program staff.

Neither the infecting *Brucella* sp nor suspected route of exposure is included in current routine national case reporting for human disease. National epidemiologic evaluations have not been conducted since the 1970s, likely because of the low incidence of human brucellosis in the United States subsequent to successful animal control programs. Targeted studies[65–68] have been conducted in Texas and California; because these states report a large proportion of the national cases, changes in disease patterns in these areas likely approximate the national situation. These studies identified a shift in risk factors from occupational to foodborne exposure—predominantly consumption of unpasteurized Mexican-style cheese—and a strong association with Hispanic ethnicity. Most infections in these states involved *B abortus* or *B melitensis,* and the distribution of cases attributed to the 2 species changed over time. In a study[65] in California in which *Brucella* isolates from 1973 through 1992 were examined, 79% of isolates for which species identification was available were *B melitensis*; in a similar study[68] conducted in Southern California, researchers reported 73% of isolates for which a species was identified from 1994 through 2002 were *B abortus*.[65–68] Current risk factors for brucellosis among humans in the United States include consumption of unpasteurized dairy products from other countries (particularly Mexico), recent recreational travel or military deployment to countries in which brucellosis is enzootic, direct contact with infected animals (predominantly wildlife [especially feral swine]), and laboratory exposure to *Brucella* organisms.[65,69,70]

Pathogenesis

Brucella spp are facultative intracellular pathogens and establish infection by invading macrophages and evading macrophage-induced host protection mechanisms.[71,72] These characteristics contribute to clinical signs and therapeutic considerations, including the difficulty in both diagnosis and treatment. Following exposure in humans, the organisms travel along the lymphatic pathways; focal disease is most commonly identified in the reticuloendothelial tissues such as the liver and spleen. In chronic infections, organisms typically localize in joints, especially large joints such as the sacroiliac or lumbar vertebral joints. Pulmonary disease is a less common form of brucellosis.[73]

In most nonhuman animals, after ingestion of the organism, the bacteria travel through the oral mucosa to the regional lymph nodes. Infection leads to bacteremia, which is usually transient; the organisms ultimately settle in the reproductive tissues or musculoskeletal system.[36,38,71] In dogs and rams, venereally transmitted organisms establish chronic infections in the testes and epididymides; infection of the reproductive tissues of females of these species may occur (more commonly in bitches and uncommonly in ewes), the pathogenesis being similar to that in large animals.[49,74]

Clinical Features

Brucellosis is frequently an insidious disease, and initial signs are generally nonspecific, regardless of species infected. In humans, the incubation period for brucellosis is typically 2 to 3 weeks, but can vary from 5 days to more than 5 months. Acute infection can be unrecognized and can result in chronic infection with symptoms recurring years later. Most common symptoms include cyclically recurring (undulant) fever, night sweats, and neuropsychiatric symptoms such as headache. Common symptoms also include malaise, sleeplessness, and arthralgias. Specific clinical signs are less common than systemic signs: arthritis, organ involvement, and genitourinary signs develop, generally in that order of frequency. Spontaneous abortions can occur among pregnant women.[75] Endocarditis, the most severe complication and most commonly associated with *B melitensis* infection, is rare (< 2% of cases), but accounts for most (80%) deaths.[76] Rates of endocarditis may be higher in regions where *B melitensis* is endemic.[77] Clinical signs can vary depending on the *Brucella* sp that is causing the infection. In a recent study[68] of US patients with brucellosis, *B melitensis* infection was more likely to cause acute, systemic disease than infections with other *Brucella* spp. In 1 US study,[68] patients infected with *B melitensis* initially developed fever (classified as fever of unknown origin) and were more likely to have organomegaly and clinically important hematologic findings, including low WBC count and thrombocytopenia, than were patients infected with *B abortus*. Case reports from outside the United States have also indicated that illnesses associated with *B melitensis* and *B suis* are more severe than those associated with *B abortus*.

In nonhuman animals, the disease can also be insidious, with clinical signs suggestive of localized infection. In livestock species (cattle, sheep, goats, and swine), the most frequent clinical sign following infection with a smooth strain of *Brucella* is often abortion.[36] Swine may also develop orchitis, lameness, hind limb paralysis, or spondylitis; occasionally, metritis or abscesses develop. Infection with *B ovis* in sheep typically results in epididymitis or orchitis, and placentitis or abortions occur infrequently. Dogs infected with *B canis* may have initial signs of general reproductive tract disorders, including abortions during the last third of a pregnancy, stillbirths, or conception failures. However, *Brucella*-infected dogs may also have initial signs of non–reproductive tract–related conditions, including ocular, musculoskeletal, or dermatologic lesions.[36,49]

Diagnosis of Brucellosis

In the United States, serologic testing is the mainstay of diagnosis in humans. Screening for brucellosis is commonly performed by use of an analyte-specific reagent ELISA in commercial laboratories. The ELISA detects antibodies against the S-LPS derived from *B abortus*; these antibodies react equally with the S-LPS of *B abortus*, *B melitensis*, and *B suis*. Immunoglobulin M against S-LPS can be detected as early as the first week of the infection, followed by detection of S-LPS–specific IgG in the second week. Concentrations of both IgM and IgG peak approximately 1 month after infection; IgM concentrations are higher than IgG concentrations at all times. Both immunoglobulins can persist for a year or more after infection, particularly if chronic infection is established.[78] Individuals with ongoing exposure to *Brucella* organisms can maintain high antibody titers in the absence of active infection. Culture of the organism from blood, bone, or samples from other sterile sites remains the gold standard for diagnosis of the disease in humans, yet cannot practically be used as a screening test. Despite its high specificity, bacterial culture has poor sensitivity for detection of *Brucella* spp, yielding organisms in samples from only 15% to 70% of acutely infected individuals and an even lower proportion of chronically infected persons.

The sensitivity and specificity of ELISAs for diagnosis of human brucellosis in endemic areas can be high,[79] but can generate false-positive results in regions of low endemicity such as the United States; results from these tests should always be confirmed. False-positive results can occur because of cross-reactions with antigens from other organisms, especially *Yersinia enterocolitica* O9 and to a lesser degree other bacteria with LPS-rich outer membranes, such as *Escherichia coli* and *Vibrio cholera*.[78,80] Confirmation of positive screening test results is best done via assessment of serum microagglutination titers. Because brucellosis in humans is uncommon in the United States and serologic results can be difficult to interpret, the most effective and accurate serologic testing should be driven by compatible clinical illness and epidemiologic history.

Diagnosis of human infection with *B canis* is more challenging. Failure to diagnose the disease may occur because illness can be nonspecific and much less severe than that caused by the smooth *Brucella* spp and because the routine serologic tests directed at detection of S-LPS would not identify infection with *B canis*.[56,81] Testing for *B canis* infection by use of experimental serologic assays[81–83] may be worthwhile for patients that have illness consistent with brucellosis, risk factors consistent with *B canis* infection, and negative results of routine serologic tests for brucellosis.[81]

Testing for brucellosis among livestock is predominantly conducted as a component of the disease eradication and surveillance program rather than as diagnostic support. Serologic testing for brucellosis in livestock is regulated by Title 9 of the Code of Federal Regulations, Part 78.[84] Two primary methods of testing are used: the *Brucella* ring test and the market cattle identification blood test. The former is a test to detect antibody in pooled milk samples from dairy herds. The latter is used to test for serum antibodies in blood samples collected from cattle and bison ≥ 2 years of age; these samples may be collected either at slaughter or as part of herd testing.[85] Those animals in which presumptive tests yield positive results are retested with the card test, the standard plate test, the tube agglutination test, or other official tests. All samples that yield positive results by use of the card test, standard plate test, or tube agglutination test are reported as market cattle identification reactors and traced to the herd of origin.[39] Challenges in the diagnosis of *B canis* infection in dogs are similar to those in humans. Bacterial

culture of blood samples to identify the organism is the gold standard and should be used as the confirmatory diagnostic test. A variety of methods have been used for serologic diagnosis in dogs, including indirect ELISA, variations of the rapid slide agglutination test, and immunochromatographic assays.[86–88] Serologic tests have variable sensitivity and specificity for the detection of brucellosis, and results pose some interpretation challenges. Practitioners conducting serologic assessments for diagnosis of brucellosis in dogs should have detailed knowledge of the nature and performance of the tests being used.[49,50,89]

Treatment

For humans with acute brucellosis, a minimum of 6 weeks of treatment is required.[90,91] The standard recommended oral treatment regimen includes doxycycline (100 mg, PO, q 12 h) in combination with rifampin (600 to 900 mg, PO, q 24 h) for a 6-week period. An alternate recommended regimen includes administration of doxycycline (100 mg, PO, q 12 h) for 6 weeks in combination with streptomycin (15 mg/kg [6.8 mg/lb] or 1 g, IM, q 24 h) for 2 to 3 weeks. Although the latter regimen is identified as the gold-standard treatment and is more effective at preventing relapses, it is less practical because the streptomycin must be administered parenterally.[92] A combination of doxycycline treatment (6 weeks' duration) with parenterally administered gentamicin (5 mg/kg [2.3 mg/lb], IM, q 24 h) for 7 days is considered an acceptable alternate regimen; few other regimens have higher efficacy than the recommended regimens.[90,93] Because of their intracellular niche and potential for slow growth rates, *Brucella* spp–associated infections may require protracted treatment. Treatment of chronic disease usually involves extended courses of antimicrobial agents, occasionally in combination with surgery to resolve focal, sequestered infections.[93,94] Relapses can occur in 5% to 15% of uncomplicated cases, usually in association with the difficulty of maintaining treatment for the specified period; monotherapy can lead to relapse rates as high as 50%.[93] Postexposure prophylaxis (eg, following laboratory exposure) should include treatment with doxycycline (100 mg, PO, q 12 h) and rifampin (600 mg, PO, q 24 h) for 3 weeks. For persons with contraindications for doxycycline (eg, pregnant women), trimethoprim-sulfamethoxazole may be considered as an alternative antimicrobial in consultation with their health-care providers. The *B abortus* RB51 vaccine strain was developed from a rifampin-resistant strain; prophylaxis or treatment required as a result of exposure to *B abortus* RB51 should therefore not include rifampin.[22]

Treatment of brucellosis in nonhuman animals is rarely recommended or effective when undertaken. Among domestic food animals, treatment is not an option given disease eradication goals; thus, infected animals are slaughtered. Exceptions for wildlife would be rare and only potentially feasible for protected species in captive zoo settings. Treatment of dogs with *B canis* infections is also not recommended, and no identified regimen has been established. For situations in which treatment is considered—for example, in breeding facilities where *B canis* has become established—regimens under investigation include oral administration of enrofloxacin (5 mg/kg, PO, q 12 h for 30 days) and additional regimens including various combinations of orally or parenterally administered gentamicin, ciprofloxacin, and doxycycline.[49,95] Single antimicrobial regimens have not been proven effective. Disadvantages of treatment include the expense of the antimicrobials, the lengthy treatment period with potential for multiple required courses, declining owner compliance, uncertain results, and ongoing public health risks.[50]

Brucella spp as Agents of Bioterrorism

Brucella suis was among the earliest agents investigated and developed as a bioterrorism weapon in the United States offensive bioterrorism program in the 1950s.[96] The zoonotic pathogens *B abortus*, *B melitensis*, and *B suis* have been identified as Category B bioterrorism agents[97] because they are easily capable of causing considerable morbidity and low numbers of deaths if used in a mass event. These 3 *Brucella* spp are also designated as select agents by the US Government.[98] They are under joint regulation between the CDC and the USDA[99] as pathogens capable of causing substantial morbidity and death rates among domestic animals, with resultant effects on food supply. Therefore, any research or other work with these pathogens, and any interstate transportation of isolates, must be registered with these regulating agencies and be accompanied by the appropriate permits.

Prevention

In almost all countries, effective prevention of brucellosis among humans and other animals is based on disease control programs in domestic animals involving vaccination and slaughter of infected animals. Several vaccines for use in nonhuman animals have been developed over the years, the most effective of which are live attenuated *Brucella* vaccines[100]; generally, each has efficacy against a specific *Brucella* sp and only in certain animal species. For cattle, the initial vaccine against *B abortus* was based on an attenuated smooth *B abortus* strain 19. This vaccine was replaced in 1996 by RB51, a vaccine that was based on a rough strain *B abortus*. Although it is a live attenuated *Brucella* vaccine, it is based on the RB51 strain, which lacks S-LPS, has much lower pathogenicity in vaccinates, is considered only mildly abortifacient, and is presumed to have much lower pathogenicity in humans in response to accidental exposure. In addition, the *B abortus* RB51 vaccine has a substantial advantage in animal disease control programs because it does not elicit an antibody response against S-LPS and does not therefore interfere with results of serologic testing.

A live attenuated *Brucella* vaccine based on a smooth variant of *B melitensis* Rev-1 appears to be highly effective and is widely used to vaccinate small ruminants in parts of the world where *B melitensis* is enzootic, including Mexico. Immunization of young recently weaned rams (weaner rams) with the *B melitensis* Rev-1 vaccine has also been recommended for control of *B ovis* in some countries; however, it is not approved for that use in the United States.[36] Like the strain 19 vaccine, this vaccine is capable of causing abortions in

pregnant animals and short-term shedding of the Rev-1 strain in milk.[101] This has led to human infections with *B melitensis* Rev-1 in Israel and the Middle East.[17,101,102] To date, no effective vaccines against *B suis* or *B canis* have been identified for use in any animal species. Although advances in vaccine safety have been made, even the current effective nonhuman animal vaccines are capable of causing both abortion among pregnant vaccinates and persistent infection among vaccinates with the vaccine strain; thus, additional improvements, including expansion of the available vaccines to include use in more animal species, and efficacy against more of the pathogenic *Brucella* spp are still needed.[103]

Control among wildlife species is more challenging, in part because of the desire to protect certain species. Brucellosis control in elk and bison in the Greater Yellowstone Area currently calls for surveillance and removal of seropositive animals from some populations as well as management actions to limit contact between bison and cattle in selected locations. Because transmission is increased among populations that access elk winter feeding areas, some authorities have proposed discontinuation of winter feeding programs. Experimental vaccination has not proven effective in feral swine or elk[104] and has shown only variable effectiveness in bison. Even when effective vaccines are developed, a large challenge for brucellosis control in wildlife and feral domestic animals remains, namely development of effective vaccine delivery systems, including oral and ballistic vaccination strategies.

Although control of brucellosis has virtually always resulted from effective animal control programs, such programs may not always be feasible, and additional efforts are necessary. No vaccine for use in humans exists, although attempts to identify a promising product have been made. Because the definitive correlates of protection for brucellosis are not known, human vaccine development remains a challenge. In areas where brucellosis is enzootic, good animal husbandry is a critical component to prevent transmission both among nonhuman animals and between other animals and humans. In the management of groups of domestic animals, careful handling of products of conception, provision of dedicated birthing areas, and implementation of good management practices (including standard biosecurity precautions and appropriate use of disinfectants) are important ways to minimize opportunities for transmission should an infected animal be introduced. *Brucella* spp are susceptible to many common disinfectants, including 1% sodium hypochlorite.[37] Cheeses and other foods made from unpasteurized dairy products from countries where brucellosis is enzootic should be avoided, and meat should not be consumed from animals that appear to be sick at the time of slaughter.

Caution should be taken when hunting or otherwise contacting wildlife or feral swine that may be infected with brucellosis.[105] Protective clothing, including gloves and eyewear, should be worn, and unnecessary exposure to blood and tissues (particularly reproductive organs) should be prevented. Hunters should carefully wash with soap and water whenever possible after dressing hunted animals and handling animal tissues. Meat should never be consumed from animals that appear to be sick.

Prevention of laboratory-acquired infections depends upon good laboratory practices and appropriate response to potential exposures. Any laboratory that might be performing cultures of *Brucella* spp should implement biosafety level 2 procedures; biosafety level 3 practices, containment, and equipment are recommended for laboratory manipulation of known *Brucella* isolates.[106] When brucellosis is suspected by a physician or veterinarian and bacterial culture of a specimen is requested, brucellosis should be indicated as a differential diagnosis on the submission form to help laboratory staff prevent potential exposures. All microbiology laboratories should have procedures in place for instances when a culture yields *Brucella* spp; these procedures should include assessing risk of exposure, implementing postexposure monitoring and prophylaxis as necessary, and following local disease-reporting requirements.[22] Although the *B abortus* RB51 vaccine strain is less pathogenic than wild-type *B abortus*, human illness can occur after accidental inoculation or laboratory exposure, and appropriate response measures should be taken following such exposures.[30,107]

Overview

Brucellosis has become less common in the United States than in decades past, but public health efforts to maintain and enhance brucellosis control efforts are necessary. Veterinarians continue to play a critical role in the understanding and control of zoonotic diseases and are considered key sources of information on these diseases by their clients and the general public. Thorough understanding of the natural occurrence of brucellosis in humans and other animals would ensure that astute veterinary practitioners are an important component in the public health control of this zoonotic disease. A veterinarian can use his or her knowledge to educate clients about known risk factors for brucellosis, recognize the potential for bioterrorism in unusual occurrences of brucellosis, and rapidly identify the development of brucellosis in domestic food animals in support of the national disease control efforts.

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Appendix

Human brucellosis case definition for public health surveillance.[62]

Clinical description	An illness characterized by acute or insidious onset of fever, night sweats, undue fatigue, anorexia, weight loss, headache, and arthralgia.
Laboratory criteria for diagnosis	Isolation of *Brucella* spp from a clinical specimen, 4-fold or greater increase in *Brucella* agglutination titer between acute- and convalescent-phase serum specimens obtained ≥ 2 weeks apart and studied at the same laboratory, or demonstration by immunofluorescence of *Brucella* spp in a clinical specimen.
Case classification	Probable: a clinically compatible case that is epidemiologically linked to a confirmed case or that has supportive serology (ie, *Brucella* agglutination titer ≥ 160 in 1 or more serum specimens obtained after onset of symptoms). Confirmed: a clinically compatible illness that is laboratory confirmed.