A one-health review on brucellosis in the United States

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ABSTRACT
Brucellosis is a highly infectious zoonotic disease of global significance due to its adverse impact on public health, economics, and trade. Despite being one of the most prevalent zoonoses worldwide, attention given to global brucellosis control and prevention has been inadequate. Brucella species of greatest one-health relevance in the US include those infecting dogs (Brucella canis), swine (Brucella suis), and cattle and domestic bison (Brucella abortus). Although not endemic in the US, Brucella melitensis warrants awareness as it poses a risk to international travelers. While brucellosis has been eradicated from domestic livestock in the US, its detection in US companion animals (B canis) and US wildlife reservoirs (B suis and B abortus) and enzootic presence internationally pose a threat to human and animal health, warranting its spotlight on the one-health stage. The challenges of B canis diagnosis in humans and dogs is addressed in more detail in the companion Currents in One Health by Guarino et al, AJVR, April 2023. Human consumption of unpasteurized dairy products and occupational exposure of laboratory diagnosticians, veterinarians, and animal care providers are responsible for human exposures reported to the US CDC. Diagnosis and treatment of brucellosis is challenging due to the limitations of diagnostic assays and the tendency of Brucella spp to produce nonspecific, insidious clinical signs and evade antimicrobial therapy, making prevention essential. This review will focus on zoonotic considerations for Brucella spp found within the US along with their epidemiology, pathophysiology, clinical presentation, treatment, and control strategies.

Brucellosis is a highly infectious zoonotic disease of global significance caused by bacteria of the genus Brucella spp. Despite being one of the most prevalent zoonoses worldwide, the World Health Organization considers brucellosis a neglected disease due to its lack of attention by global health systems.2 Brucellosis is a priority disease of the World Organization for Animal Health (WOAH) owing to its worldwide adverse impact on public health, economics, and global trade.3 The Brucella genus includes 13 species infecting a range of susceptible hosts, but those of greatest one-health relevance in the US include species infecting dogs (Brucella canis), swine (Brucella suis), and cattle and domestic bison (Brucella abortus). Although not endemic in the US, Brucella melitensis infects sheep and goats and poses a risk to international travelers. Brucellosis control in the US is overseen by state and federal agencies, and all human cases are reportable to the CDC. Due to the zoonotic nature of brucellosis, its management in the US requires the awareness of medical professionals in both the human health and veterinary sectors, including knowledge of the exposure risks, diagnostic limitations, treatment practices, and preventative surveillance programs in place.

Common Features of Brucella Species
Brucellae are gram-negative, facultative, intracellular rods, coccii, or coccobacilli that thrive in cool, wet conditions. They resist freezing and thawing but can be killed through pasteurization and are susceptible to most common disinfectants.4,5 Brucella spp with the highest human pathogenicity (B abortus, B melitensis, and B suis) carry an O-polysaccharide (O-PS) side chain on the lipopolysaccharide (LPS) component of the cell wall and are of the smooth colony phenotype.6 The rough colony phenotypes (B canis and Brucella ovis) lack the O-PS antigen, a feature that is used to differentiate them from smooth species on serologic assays.7 Several fundamental aspects of brucellosis epidemiology and pathophysiology are shared among Brucella species. Transmission occurs either vertically
or horizontally to offspring and via direct or indirect contact through ingestion, mucous membranes, a break in the skin, or inhalation (Figure 1). Brucella spp translocate across mucous membranes, then spread to regional lymph nodes and proliferate within macrophages, where they evade macrophage-induced defense mechanisms. Hematogenous spread of Brucella spp to other tissues follows, with a marked tropism for the gravid uterus and placenta. Tropism for placental trophoblasts is thought to be secondary to high concentrations of erythritol, which can be metabolized by Brucella spp as a source of carbon and energy. Brucella spp can travel throughout the body, including tissues of the reticuloendothelial system (lymph nodes and spleen), mammary gland, reproductive tract, and musculoskeletal system (bone and synovial structures) and have a tendency to settle in areas of end arterial circulation (eye, kidney, meninges, and intervertebral disc). The intracellular persistence of Brucella spp facilitates evasion of the innate and adaptive host immune system and reduces exposure to antimicrobials, making treatment challenging in all host species.

The most common clinical manifestation of brucellosis in animals is abortion. Other characteristic clinical signs in female hosts include the birth of stillborn or weak offspring, retained placentas, decreased milk yield, and decreased fertility, while intact males experience orchitis, epididymitis, seminal vesiculitis, and testicular atrophy in later stages. Brucella spp are shed in postpartum vaginal discharge and milk, as well as sporadically in urine and semen, making contact with these bodily fluids an exposure risk (Figure 1). The shedding of Brucella spp in milk and vaginal discharge accompanies both abnormal births and normal parturition in asymptomatic carriers and can last for weeks to months beyond parturition, thereby contributing to the spread of brucellosis within a population. Following brucellosis abortion, affected animals can have subsequent normal births, with the possibility of future sporadic infertility issues and abortions. Offspring that acquire Brucella spp infection vertically or through ingestion of milk may be serologically negative and asymptomatic. These animals with latent asymptomatic infection can abort or give birth to their own infected offspring and

### Brucellosis Transmission in the United States

![Diagram of brucellosis transmission](image)

Figure 1—Primary modes of human and animal brucellosis transmission in the US, emphasizing Brucella canis, Brucella suis, and Brucella abortus. Printed with permission from the Cornell University College of Veterinary Medicine.
play an important role in maintaining disease within a population. Abscesses and histologic evidence of granulomatous inflammation can be seen in affected organs and tissues. While reproductive failure is a hallmark of brucellosis, in many human and animal cases the diagnosis of brucellosis is complicated by a slow and insidious progression, characterized by nonspecific clinical signs such as lethargy, malaise, musculoskeletal pain, anorexia, and weight loss.

Bacterial culture is the gold standard to definitively diagnose brucellosis, followed by identification with biochemical tests or matrix-assisted laser desorption/ionization time of flight mass spectrometry. Ideal samples for culture are the aborted fetus and placenta, particularly fetal lung and stomach contents. Useful ante-mortem culture specimens include blood, urine, semen, and vaginal discharge. Postmortem, Brucella spp can be isolated from affected tissues collected during necropsy, including lymph nodes (particularly iliac, mammary, and prefemoral), liver, spleen, and reproductive organs. A negative culture never rules out Brucella spp infection due to the following: intermittent bacteremia and shedding; organism viability, especially associated with antimicrobial drug administration; potential for blood culture contamination; and slow growth in laboratory culture, taking up to 21 days.

PCR tests for Brucella spp are often genus based rather than species specific, although species-specific PCRs have recently been developed. PCR can be applied to whole blood, vaginal secretions, urine, semen, or tissues as listed above for culture. Sequencing of an isolate by PCR or other molecular techniques can determine biovar. A variety of serologic assays are available for brucellosis screening. The outer cell membrane of all Brucella spp is antigenically similar to other gram-negative bacteria, resulting in the production of antibodies, especially IgM, which may cross-react on serology assays to produce false-positive results. While animal infections with B abortus or B suis are reportable in all US states, B canis reporting requirements vary. Positive serology tests for smooth Brucella spp performed at accredited US laboratories are forwarded to the National Veterinary Services Laboratory in Ames, Iowa, where confirmatory testing is required. Whenever possible, positive Brucella spp serology should be confirmed with bacterial culture methods.

**Brucella canis**

**Epidemiology**

B canis primarily infects dogs and wild canids, but humans can also become infected. Globally, seroprevalence rates range in dogs from <1% to 15% or more, with higher rates associated with stray dogs and impoverished areas, likely due to higher numbers of intact dogs and uncontrolled breeding in these populations. In the US, testing for B canis is not routinely performed in most animal shelters, allowing for the potential risk of adopting a dog with undiagnosed B canis. Breeding kennels are another source of the spread of B canis, due to the increased risk of disease in intact dogs and constant close contact and movement of dogs in these facilities. The prevalence of human brucellosis due to B canis appears highly variable across different countries and populations; however, human exposure is likely under-recognized due to the lack of B canis serologic tests for humans (Figure 2).

**Figure 2**—B canis diagnostic algorithm for dogs and humans. Printed with permission from the Cornell University College of Veterinary Medicine.

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Modes of *B. canis* transmission and shedding is similar to other *Brucella* spp.; however, urine exposure plays a larger role in *B. canis* transmission in dogs as compared to other species (Figure 1). Both sexes shed *B. canis* sporadically in urine, beginning 1 to 2 months postexposure and lasting for months to years, with higher numbers typically present in urine from male dogs due to *B. canis* localization to the prostate and epididymis, which are closely associated with the bladder. Neutering can help to reduce *B. canis* transmission risk but does not fully prevent it. Venereal transmission can play a large role in the spread of *B. canis* infection in breeding kennels. Veterinarians, kennel workers, dog breeders, and laboratory personnel are at increased risk for *B. canis* exposure. Transmission to humans is most likely to occur through contact with infectious canine reproductive tissues and discharges. Contact with urine, feces, or saliva from infected dogs may also pose a risk. Additionally, laboratory personnel may be exposed through inhalation of infectious aerosols during manipulation of specimens.

**Clinical signs and diagnosis**

Humans infected with *B. canis* may develop nonspecific signs such as intermittent fever, fatigue, and lymphadenopathy. Rarely, human infections result in more severe disease manifestations such as polyarthritis, meningitis, or endocarditis. Reproductive outcomes in dogs infected with *B. canis* are similar to those of other *Brucella* spp. Abortions occur most commonly between 45 and 60 days of gestation. Parturition at full term may include both apparently healthy and weak puppies in the same litter. While discospondylitis, reproductive failure in the bitch, and genital tract abnormalities in the male are pathognomonic clinical signs for *B. canis* in dogs, it is critical for practitioners to understand that nonspecific clinical signs are also common. *B. canis* should be included as a differential when the patient is young and has a history of recent rescue or importation or is part of a breeding kennel. Nonspecific clinical signs in dogs may include lethargy, weight loss, lameness, and exercise intolerance, along with findings of lymphadenopathy or splenomegaly. Following intermittent episodes of bacteremia beginning 7 to 30 days postinfection, *B. canis* may travel hematogenously to the intervertebral disc, eye, or meninges, manifesting as uveitis, granulomatous chorioretinitis and discospondylitis, or sacroiliitis. Dogs with discospondylitis often present with intermittent back pain, intermittent lameness, paresis, and lethargy. Spontaneous recovery from *B. canis* is possible in 1 to 5 years, but other dogs may remain chronically infected.

Diagnosing *B. canis* infections in humans is very challenging due to the lack of validated serologic tests for humans in the US. Culture or PCR remain the only means of diagnosing *B. canis* in humans, likely resulting in this zoonotic disease being vastly underdiagnosed. In 2022, the popular D-Tec CB point-of-care *B. canis* screening kit manufactured by Zoetis for use in dogs became unavailable, shifting screening serology for dogs to reference veterinary diagnostic laboratories and prolonging result turnaround times. Lateral flow immunochromatographic assays are available for point-of-care use by veterinarians; however, insufficient studies are available to evaluate their accuracy. Reference veterinary diagnostic laboratories offer other serologic screening tests including the canine *Brucella* multiplex assay (CBM), indirect fluorescent antibody test, tube agglutination test, rapid slide agglutination test (RSAT), and surface antigen-based agar gel immunodiffusion (AGID) assays (Figure 2). With the exception of the CBM, these tests typically detect LPS cell wall antigen and are more prone to cross-reactivity with other gram-negative bacteria, resulting in poor specificity. By adding 2-mercaptoethanol to the RSAT or tube agglutination test, IgM antibodies and other nonspecific agglutinins are dissociated, increasing their specificity. The CBM assay offers the benefit of being both quantitative and more specific by detecting antibodies to 2 *Brucella*-specific antigens, BP26 and PO1, rather than LPS cell wall antigen. The CBM assay is further addressed in the companion Currents in One Health by Guarino et al, *AJVR*, April 2023. Several ELISAs have been designed for the detection of *B. canis* antibodies as well, but the sensitivity and specificity vary widely depending on the antigen used.

False-negative screening serology results in dogs can occur under several conditions, including if a dog is tested prior to seroconversion, cases of chronic infection, dogs under 6 months of age when seroconversion is delayed by colostral-derived antibodies, and when the 2-mercaptoethanol-RSAT test is run in acutely infected dogs when IgM predominates early in infection. A positive test result on any of these screening assays must be confirmed with the more specific cytoplasmic antigen-based AGID test (AGID II), which is only available at reference veterinary diagnostic laboratories (Figure 2). Infected dogs typically seroconvert 2 to 12 weeks postinfection. The RSAT can detect early infections, starting at around 3 to 4 weeks, and the AGID test may take 8 to 12 weeks to become positive. Consultation with a state animal health official for *B. canis* testing strategy guidance is encouraged to help avoid improper test interpretation that can result in failure to identify infected dogs and thereby expose additional susceptible animals or falsely diagnose dogs, leading to unnecessary euthanasia.

While imaging studies can assist in the diagnostic work-up for dogs presenting with clinical signs of discospondylitis, serum C-reactive protein concentrations can also be helpful as a nonspecific biomarker for discospondylitis. Aqueous humor, bone marrow aspirates, and CSF are suitable sample types for culture and PCR confirmation of cases with uveitis, discospondylitis/osteomyelitis, or meningoencephalitis, respectively.

**Treatment and prevention**

Elimination of canine *B. canis* infections despite use of antimicrobials is not always possible, and persistent infections are common. Due to the zoonotic
risk posed by *B. canis*-infected dogs, euthanasia is often elected. When treatment is attempted, neutering is always required first to decrease shedding. There is no universally accepted antimicrobial treatment protocol for *B. canis* in dogs, but combination antimicrobial therapy is more effective than monotherapy, and analgesia is often required, which is addressed in the companion Currents in One Health by Guarino et al, *AJVR*, April 2023. Combinations of antimicrobials most widely utilized include a tetracycline (for the first 1 to 2 months) with an aminoglycoside (for the first 1 to 2 weeks, or two 1-week courses spaced 1 month apart). Fluoroquinolones such as enrofloxacin may be prescribed when patients do not tolerate aminoglycosides. Rifampin may also be prescribed in conjunction with these combinations of drugs to improve antimicrobial penetration.

While some dogs experience resolution of clinical signs and reduction of antibody titers after extended antimicrobial therapy utilizing multiple drug classes, this can also predispose to antimicrobial resistance in other exposed bacteria and recurrence of *B. canis* infection is common. Repeat serologic testing with a quantitative assay is indicated after cessation of treatment, as increasing titers may indicate recrudescence and the need for additional treatment. The utility of the CBM assay for monitoring response to treatment is addressed in the companion Currents in One Health by Guarino et al, *AJVR*, April 2023.

The US currently lacks federal guidelines mandating *B. canis* testing prior to interstate or international movement of dogs, despite evidence showing that *B. canis* has been introduced to nonendemic countries through the importation of infected dogs and spread interstate through animal adoption, dog rescues, and breeders in the US. Ideally, dogs should be tested for *B. canis* prior to interstate or international movement, especially for breeding purposes. In the absence of a *B. canis* vaccine, other prevention strategies remain the most effective means of controlling *B. canis*. Owners, breeders, kennel employees, and veterinarians must be properly educated to recognize *B. canis* clinical suspects and promote prevention strategies, including screening tests for dogs suspected of having brucellosis, treatment or euthanasia of dogs confirmed to be infected with *B. canis*, and appropriate cleaning and disinfection strategies to eliminate the bacteria from the environment.

For breeding operations, serial screening of the kennel population with removal of infected dogs and repeated testing of new additions is essential. Any kennel that does not have a closed population should screen all dogs 2 to 4 times per year at minimum. New dogs should be isolated and screening serology performed twice, 12 weeks apart, to account for the seroconversion period. The confirmation of a single *B. canis* case in a kennel setting necessitates screening the remaining dogs.

The National Association of State Public Health Veterinarians published a position statement on human *B. canis* infections in 2012 asserting that canine brucellosis should be more widely notifiable in the US to prompt public health responses and identify additional human exposures. Prevention of disease in humans should involve owner education about the zoonotic risks of *B. canis*. Some owners may opt to prevent risk through euthanasia of infected dogs. Others may take an approach of minimizing exposure risk through neutering, treating with appropriate antimicrobial therapy, and continued serologic monitoring. This does not eliminate the ability for a dog to shed organism, and personal protective equipment (PPE) should still be used when handling high-risk specimens such as urine and feces from infected dogs.

In addition, the National Association of State Public Health Veterinarians position statement encourages the CDC to narrow the knowledge gap surrounding human *B. canis* infections by requiring *Brucella* spp. speciation in every human case and encouraging the CDC, NIH, and other partners to work toward the development of serologic tests for *B. canis* in humans. The AVMA policy on *B. canis* likewise advocates for the development of validated serologic assays for humans. It is clear that a more unified approach between local, regional, and federal agencies to develop *B. canis* management guidelines is a critical next step.

### Brucella suis

#### Epidemiology

*B. suis* biovars 1, 3, and 4 are found in the US. Swine are the reservoir host for biovars 1 through 3, but infections occur in humans, cattle, and occasionally other species. *B. suis* biovar 4 is found in caribou and reindeer in arctic regions, including Alaska. In 2011, *B. suis* was eradicated from US commercial swine, but remains in feral swine, particularly in the Southern and Western US, and poses a continued risk to commercial swine operations (Figure 1). As of 2021, feral swine were present in 38 US states, including high pork-producing states. The current feral swine population is over 6 million, with 2 million in Texas alone, and estimates of seroprevalence vary greatly by geographic region. Controlling feral swine is very difficult, as they reach sexual maturity at a young age, have a short gestation period, are prolific breeders, lack natural predators, and can survive in many different environments. Transitional swine farms, defined as either captive feral pigs or farmed pigs with access to feral swine, are at risk for introducing *B. suis* into their herds.

Human cases of *B. suis* infection in the US have been linked to feral swine hunting and field dressing of feral swine without proper PPE or exposure to infected transitional swine not under USDA surveillance (Figure 1). In 2016, a confirmed human case of *B. suis* in a New York swine producer resulted in an interstate epidemiologic investigation that identified 8 additional infected herds. A seropositive family member and a farm dog and her puppies were also identified on the premise. It was concluded that *B. suis* entered the index farm following purchase of *B. suis*-infected swine from a herd in contact with wild boar. This multistate, multispecies brucellosis outbreak...
demonstrates the widespread impact of this pathogen on public health, wildlife, and domestic animals (A. Newman, DVM, MPH, DACVP, New York State Department of Health, email, November 21, 2022).

Clinical signs and diagnosis

The mode of transmission and clinical signs of *B. suis* are similar to those of other *Brucella* spp. Nonreproductive clinical signs in pigs include arthritis, discospondylitis, lameness, and posterior paralysis.21,72 *B. suis* infection should be considered for dogs used for feral swine hunting, dogs that roam free in areas that have feral swine populations, and their sexual contacts.72–75 *B. suis* can also be a risk to dogs fed raw meat from US feral swine or imported raw meat from countries that are not brucellosis free (Figure 1).72 Clinical signs in dogs with *B. suis* are similar to *B. canis* infections.71 *B. suis* is second to *B. melitensis* in human pathogenicity.76 Human *B. suis* infection can be insidious in onset, and clinical signs include fever, fatigue, night sweats, malaise, myalgia, and respiratory signs in the acute phase, followed by cardiac issues, osteoarthritis, and neurologic symptoms in chronic cases.29,77

The serology assays available for *B. suis* screening in swine cross-react with other smooth colony *Brucella* spp (*B. abortus* and *B. melitensis*).21 The available serology tests include buffered acidified plate antigen (BAPA), fluorescence polarization assay (FPA), competitive ELISA, tube agglutination, plate agglutination, and complement fixation.30 Published data show great variation in sensitivity and specificity for *B. suis* serology assays,21 and prevalence studies performed in the US have shown serology to be less sensitive than culture for surveillance of *B. suis* in feral swine.30,31,68,78 If a swine-hunting dog is suspected of having *B. suis*, culture of blood or affected tissue provides a definitive diagnosis. Serologic testing for the smooth colony phenotype is not validated on canine serum, making *B. suis* infection in dogs a potentially difficult diagnosis. Human diagnosis of *B. suis* can be made by culture or serology testing.23

Treatment and prevention

Treatment is not recommended for *B. suis* in pigs, and reported infections in dogs have resulted in euthanasia.22,73,75,79 Swine brucellosis is reportable, and herd depopulation will be mandated by state and federal regulatory agencies when detected in the US.80 There is currently no vaccine available for *B. suis* in the US.

Ongoing surveillance for swine brucellosis occurs through the USDA APHIS.81 Swine producers may participate in Validated Qualified herd testing programs, which involve routine serologic screening of breeding-age pigs.82 The USDA APHIS allocated funding from the 2018 Farm Bill to initiate the Feral Swine Eradication and Control Program. The goals are to remove feral swine, repair damaged natural resources, and assist domestic swine farmers.82 Preventative measures for mitigating transmission of *B. suis* from feral swine to domestic farm animals include housing pigs inside and providing double fencing. Some states encourage hunting of feral swine for population control, but hunting dogs should be monitored for clinical signs of *B. suis*. Veterinarians servicing transitional swine herds and farmers purchasing swine from herds that are not enrolled in the Validated Qualified swine herd testing program should monitor for *B. suis* clinical signs.23

**Brucella abortus**

Epidemiology

*B. abortus* is primarily a disease of cattle and bison but has also been reported in yak and wildlife species (eg, elk, sika deer, African buffalo, and antelope), as well as horses, camels, and South American camelids in contact with infected ruminants.3,28 While *B. abortus* biovar 1 was once considered the most significant livestock disease in the US, causing high rates of human infection through contact with infected animals or consumption of unpasteurized dairy products, it has now been eradicated from US cattle and domestic bison.84,85 The US brucellosis Class Free status is preserved through ongoing cooperative efforts between the USDA APHIS, cattle producers, and state animal health authorities.86–88

*B. abortus* remains enzootic in regions of Europe, Central and South America, Africa, and Asia, where its prevalence is associated with reduced availability of economic resources, increased implementation of surveillance programs and control policies, and large bovine populations.89

Modes of *B. abortus* transmission in ruminants are similar to other *Brucella* spp,1,3,23,50 and ingestion is the most common route of infection in cattle.91 *B. abortus* is shed in the milk of infected cattle throughout life.24,25 *B. abortus* live attenuated RB51 vaccine can also be shed in milk even when administered per label instructions and is a source of infection for people in the US consuming unpasteurized milk (Figure 1).92 Environmental contamination by *B. abortus* at birthing sites allows susceptible animals to become infected when grazing contaminated areas. Bacteria are killed in the environment through drying and UV light exposure or removed following scavenging of aborted tissues by predators.93

The persistence of *B. abortus* in US wildlife reservoirs requires ongoing collaborative management by state and federal agencies to prevent exposure and resurgence in livestock. *B. abortus* is endemic in wild herds of elk and bison in the Greater Yellowstone Area (GYA), which encompasses 28,000 square miles within Idaho, Montana, and Wyoming.94 Current management practices of bison within Yellowstone National Park prevent spatiotemporal overlap between bison and cattle.95 However, free-ranging cattle and domestic bison of the GYA share habitat with wild elk and are therefore at risk for *B. abortus* exposure (Figure 1).94,96,97 Late January to May is the most likely period for *B. abortus* transmission between elk, bison, and cattle because it contains their calving season, including the last 90 days of gestation when
late-term abortion might occur. The greatest risk of cattle and domestic bison exposure occurs when elk abort preterm, during a period when the elk congregate in groups at lower-elevation winter habitat that overlaps with cattle grazing areas. The behavior of bison to gather and nuzzle newborn calves allows B abortus to remain endemic within Yellowstone National Park herds. Suplemental winter feeding of elk in the GYA controls elk distribution away from livestock, but doing so has increased the elk population density, leading to unflc elk exposure and increased risk of interspecies B abortus transmission.

Clinical signs and diagnosis
Clinical manifestations of B abortus in cattle mimic Brucella spp infection in other species. In addition to aforementioned organs harboring Brucella spp, it can sometimes be isolated from hygromas in cattle. Infected bulls are often asymptomatic but rarely develop systemic signs of fever, inappetence, and depression. B abortus is among the etiologic agents found in association with the conditions poll evil and fistulous withers in horses and should be considered when horses live with infected livestock.

In the US, surveillance serologic testing for B abortus must be performed by a federally accredited veterinarian through an approved brucellosis laboratory using a series of 2 tests, including the BAPA assay and the FPA, which detect antibodies against B abortus strain 1119-3 and cell wall O-PS antigen, respectively. These assays are run in series to improve sensitivity and specificity, and positive tests are followed by complement fixation for epidemiologic classification. The FPA is fully automated compared to the manually run BAPA, allowing its efficient use for high-volume surveillance testing. A variety of other B abortus serologic assays are available for cattle and may be required for export. Culture, PCR, and experimental dot blot assays have been used to differentiate infection caused by RB51 vaccine strain from wild-type B abortus in cattle.

Treatment and prevention
Treatment for B abortus in livestock is not recommended due to the risk of bacterial persistence following treatment and potential negative impact of resurgence on international trade, food safety, and public health. Instead, infected livestock are culled. The prevention of B abortus within herds involves the use of an approved vaccine (RB51 in the US) and targeted biosecurity, such as serologic screening of new stock, prevention of contact with wildlife reservoirs, infected herds or those of unknown brucellosis status, performing diagnostic investigations following abortions, proper disposal of placentas and nonviable fetuses through burial or burning, and disinfection of contaminated areas. Vaccination is considered the most important method of B abortus control in livestock. In 1996, APHIS replaced the original B abortus live attenuated strain 19 vaccine with RB51 for use in US cattle, to be administered SC to nonpregnant heifers between 4 and 12 months of age. The RB51 live attenuated vaccine was developed using a rough, rifampin-resistant B abortus strain that does not express O-PS on its membrane, thereby preventing its cross-reaction on serologic assays.

All livestock vaccinated with RB51 receive official permanent USDA ear tag and tattoo identification. RB51 vaccine is contraindicated in pregnant cattle, as it can induce abortion and increase perinatal mortality. Exposure of livestock to large doses of B abortus can overwhelm vaccine-induced immunity and result in infection. Rare instances of B abortus strain 19 and RB51 have been found in US feral swine in contact with vaccinated cattle. The United States Animal Health Association encourages state animal health officials and cattle industry representatives to only use RB51 vaccination for livestock in areas where infected wildlife exposure is a documented risk. They also promote the use of interstate brucellosis vaccination requirements on the basis of whether animals are moving into, within, or out of the GYA.

The persistence of B abortus in elk and bison of the GYA prevents complete US eradication. Ongoing B abortus surveillance under the Brucellosis Emergency Action Plan and USDA’s National Brucellosis Surveillance Program is largely risk based, focusing slaughter testing on animals originating from the GYA, but also employs surveillance of cattle strays along the US-Mexico border, passive surveillance by accredited veterinarians reporting clinical cases, targeted livestock market surveillance of cattle with reproductive issues, and export-related surveillance. Each GYA state works with state animal health partners and fish and game departments to develop a Brucellosis Management Plan. While no specific federal regulations exist for brucellosis control in farmed cervids, many states administer cervid herd brucellosis accreditation programs, which can facilitate interstate movements. Continued surveillance is critical for the prevention of B abortus resurgence in US livestock, to protect public health and food safety, and to demonstrate ongoing disease-free status to international trade partners and the WOAH.

Other Brucella Species
B melitensis is not present in the US but is endemic in Asia, the Middle East, South America, and Africa. B melitensis is responsible for most of the global human brucellosis cases, with an estimated 500,000 cases per year worldwide. B melitensis has a smooth colony phenotype with 3 biovars. Sheep and goats are the reservoir hosts, but it has been found in a variety of other species. Clinical signs and routes of transmission for B melitensis in small ruminants are similar to Brucella spp in other host species. The melitensis eradication programs utilized internationally employ test and slaughter in conjunction with the modified live Rev-1 vaccine. The 3% rose bengal and complement fixation tests are used to detect B melitensis antibodies.

Sheep are the reservoir host for B ovis, which is endemic in the US but not zoonotic. Transmission and clinical signs are similar to other Brucella.

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spp.\textsuperscript{121,122} and no vaccine exists. Serologic screening assays are available, including ELISA.\textsuperscript{121-123}

There are 8 remaining recognized \textit{Brucella} spp including \textit{Brucella neotomae} (wood rats),\textsuperscript{124} \textit{Brucella microti} (voles),\textsuperscript{125} \textit{Brucella inopinata} (human),\textsuperscript{126} \textit{Brucella amazoniensis} (human),\textsuperscript{127} \textit{Brucella ceti} (cetaceans), \textit{Brucella pinnipediales} (pinnipeds),\textsuperscript{128} \textit{Brucella papionis} (baboons),\textsuperscript{129} and \textit{Brucella vulpis} (red foxes).\textsuperscript{130} \textit{B ceti} causes clinical signs similar to other \textit{Brucella} spp, along with blubber abscesses.\textsuperscript{130,131} Diagnosis is made by culturing tissues, and a competitive ELISA is available.\textsuperscript{122}

\textbf{\textit{Brucella} spp Zoonotic Considerations}

\textbf{Epidemiology}

From 2000 to 2019, the number of brucellosis cases reported annually in the US ranged from 79 to 165 annually, down from its peak of 6,000 annual cases prior to federal eradication efforts.\textsuperscript{84,133} Transmission to humans may occur following occupational exposure as a laboratory diagnostician, veterinarian, animal care worker/breeder, or human medical provider or through the consumption of unpasteurized dairy products, particularly during travel outside the US (Figure 1).\textsuperscript{29,41,45,106,134} \textit{Brucella} spp are easily aerosolized, making the handling of specimens outside a biosafety cabinet a significant risk for laboratory diagnostician exposure.\textsuperscript{43,135} The high human pathogenicity of the smooth \textit{Brucella} spp, their tendency for aerosolization, and low infectious dose of 10 to 100 microorganisms gives them potential as weapons of bioterrorism, resulting in their select agent status by the USDA and CDC.\textsuperscript{136} Children, immunosuppressed individuals, pregnant women, and HIV-positive individuals are at higher risk of developing clinical illness when infected with \textit{B canis}.\textsuperscript{138,45,137} Human-to-human brucellosis transmission is rare but can occur through congenital infection, sexual transmission, and nosocomial disease.\textsuperscript{29,138}

\textbf{Clinical signs in humans}

Brucellosis in people can have a variable incubation period, ranging from 5 days to 6 months, with an average onset of 2 to 4 weeks following exposure. Acute clinical signs can be flu-like and nonspecific (eg, fever, headache, myalgia, body aches, anorexia, and weight loss) with lymphadenopathy or splenomegaly.\textsuperscript{139,140} Chronic disease is characterized by recurrent fever and organ-based complications commonly involving the skeletal system (eg, peripheral arthritis, spondylitis, and sacroiliitis) but can also involve the cardiovascular system, respiratory system, gastrointestinal system, male genitalia, and CNS.\textsuperscript{139,140} Infection in pregnant women may result in abortion, often during the first and second trimesters, or the birth of premature infants or those with low birth weight.\textsuperscript{139,141,142}

\textbf{Diagnosis and treatment in humans}

Definitive diagnosis of the smooth \textit{Brucella} spp in people requires isolation through culture from clinical specimens or evidence of at least a 4-fold rise in antibody titer on acute and convalescent serology at least 2 weeks apart.\textsuperscript{29} No serologic assays are available for the detection of \textit{B canis} or RB51 strain \textit{B abortus} in people, making their diagnosis reliant on culture or molecular diagnostics (Figure 2). Human cases of \textit{B canis} may be significantly under-recognized due in part to the lack of validated serologic tests for humans in the US, the fact that laboratories handling human specimens do not typically have extensive experience cultivating and identifying \textit{B canis}, and the low diagnostic suspicion among many physicians.\textsuperscript{45}

The \textit{Brucella} spp microagglutination test is the confirmatory serologic test to diagnose human brucellosis and detects IgM, IgG, and IgA antibody classes produced in response to wild-type \textit{B abortus}, \textit{B suis}, and \textit{B melitensis}. Other types of enzyme immunoassay tests exist for use in people but are not quantitative and must be confirmed with the \textit{Brucella} spp microagglutination test. The use of an IgG ELISA might be beneficial when cases are chronic or when infection of the CNS is suspected.\textsuperscript{29} Similar to serologic assays used in animals, those used in people can cross-react with antibodies produced against other gram-negative bacteria, including \textit{Escherichia coli}, \textit{Francisella tularensis}, \textit{Moraxella phenylpyruvica}, \textit{Yersinia enteroxocolitica}, certain \textit{Salmonella} spp, and \textit{Vibrio cholerae} vaccine antibodies.\textsuperscript{29}

Human brucellosis treatment consists of oral combination antimicrobial therapy for a minimum of 6 weeks to decrease the incidence of relapse, often involving doxycycline with rifampin.\textsuperscript{12,143,144} An aminoglycoside antibiotic such as gentamicin or streptomycin may be added for the first 2 weeks of combination therapy in complicated human cases, including for patients experiencing endocarditis, meningitis, and osteomyelitis. In cases involving high-risk exposures, recommendations for postexposure symptom and serologic monitoring and antibiotic prophylaxis may ensue (Figure 2).\textsuperscript{29,45,135} Due to the resistance of RB51 to rifampin, combination therapy should include doxycycline and trimethoprim-sulfamethoxazole or another designated antimicrobial.\textsuperscript{29} Mortality associated with \textit{Brucella} spp infections is low (< 1%) when initiated in a timely manner and is primarily associated with endocarditis.\textsuperscript{141,145,146}

\textbf{Prevention in humans}

The use of universal precautions and PPE is critical to human occupational brucellosis prevention. Laboratory diagnosticians handling \textit{Brucella} spp are required to do so in a class II or higher biosafety cabinet.\textsuperscript{29} Veterinarians handling the live attenuated \textit{Brucella} spp vaccines (strain 19, RB51, and Rev 1) must take care during vaccine handling to prevent needle sticks or spray into open wounds or conjunctiva. Hunters of wild ungulates should avoid exposure during field dressing/butchering, and both hunters and their dogs should not consume undercooked meat. When visiting a \textit{Brucella} spp–endemic region, travelers should avoid contact with potentially infected livestock and the consumption of their undercooked meat and unpasteurized dairy products.\textsuperscript{29}
Conclusion

A one-health approach is required to manage and prevent brucellosis infections in human and veterinary species in the US. This effort will involve continued collaboration between state and federal agencies, medical professionals, and industry stakeholders to maintain brucellosis surveillance and prevention programs, recognize exposure risks and symptoms of clinical disease, utilize appropriate diagnostic strategy, and determine optimal management of confirmed cases or infected populations.

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