Review Article
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A Comprehensive Review of Bovine Brucellosis: Epidemiology, Challenges and Strategies for Effective Control

Koushik Kakoty [(1)*], Monosri Johari [(2)]

[(1)]Department of Veterinary Public Health, Lakhimpur College of Veterinary Science, Assam Agricultural University, Joyhing, North Lakhimpur,Assam- 787051, Indian [(2)]Department of Veterinary Extension Education, College of Veterinary Science, Assam Agricultural University, Khanapara, Guwahati, Assam- 781022, India

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Abstract

Brucellosis, an ancient and highly complex zoonotic disease with epidemiological dynamics that has greatly changed over the years is still a concern. The disease has extended to other areas and shown the capacity for infecting various animals involving wildlife. These problems are exacerbated by the consumption of unpasteurized dairy products made on farms lacking basic hygiene in endemic region and human-animal movements across nations that complicates tracking brucellosis spread and control even more so within high to low prevalence areas. The diagnosis is most effective by conventional pathogen identification and isolation that is less sensitive and time consuming; hence, there is a need to develop state-of-the-art diagnostic tools alongside stringent screening of newly introduced animals. Vaccination, mainly by the strains 19 and RB51, plays a key role in preventing Brucella infections and thereby reducing the complications in cattle. Coordinated brucellosis control involves continuous and persistent surveillance, especially in high-risk areas. A One Health approach is critical to comprehensive control and prevention strategies based on their interdependence with humans, animals and the environment.

Keywords: Brucellosis, Bovine, Prevention, Control

Introduction:

Brucellosis is an important zoonotic disease that presents an alarming state of health hazard for animals and humans. Bovine brucellosis is caused by several species of the Brucella bacterium, mainly *Brucella abortus*, *Brucella melitensis* and *Brucella suis* (OIE, 2018). Since this disease has the peculiarity of infection in several hosts through direct and indirect contact, it is particularly elusive to control. Contaminated feed and water, together with infected reproductive materials, are the usual sources of the transmission of brucellosis in animals, while mixed farming practices enhance the potential for transmission (CFSPH, 2018a; 2018b). Direct contacts with infected animals or unpasteurized milk products are usually the means of transmission to humans (Moreno, 2014).

Brucellosis is distributed heterogeneously across the globe. Countries in Central Asia, the Middle East and parts of Africa have higher incidence rates in comparison to other nations that seem to have taken control of this disease, such as Canada and Australia (Pappas et al., 2006). The disease remains a challenge in India because there is low public awareness of it, poor farming practices and high costs of diagnosis and vaccination (Durrani et al., 2020). National Animal Disease Control program for brucellosis has been undertaken in India for 100% vaccination of female calf (4-8 month). However effective control measures would involve enhanced surveillance, mass vaccination of animals and proper culling of infected animals (CDC, 2018). This can only be achieved through collaboration and cooperation between the veterinary and public health sectors to reduce the burden of brucellosis and prevent further spread.

Epidemiology:

The bacterium:

The Brucellae are classified recently as members of the Proteobacteria a–2 subdivision gram negative, facultative intracellular rods or coccobacilli that lack capsules, endospores and native plasmids. The bacterium is partially acid fast, with oxidase, catalase, nitrate reductase and urease activity; it is 0.5–0.7 mm in diameter and 0.6–1.5 mm in length. Brucellae are relatively resistant to freezing and thawing, while most of the disinfectants in general use are bactericidal. Under cool and especially moist conditions they can survive in the environment for several months. Although they are non-motile, they have all genes to make a flagellum. Six classic and several novel *Brucella* species have been described in various susceptible hosts. Seven species cause disease in terrestrial animals and include *B. abortus*, *B. melitensis*, *B. suis*, *B. ovis*, *B. canis*, *B. neotomae* and *B. microti*; two other species, *B. ceti* and *B. pinnipedialis*, affect marine mammals. *B. papionis* was isolated from baboons and *B. vulpis* was isolated from red foxes. *B. abortus* has seven biovars, *B. melitensis* has three and *B. suis* has five biovars.

Host range:

Brucellosis in cattle is usually due to *B. abortus*, even though *B. suis* and *B. melitensis* also cause the disease in these animals (CFSPH, 2018a; 2018b). *B. melitensis* and *B. suis* are transmitted to man by contaminated cow's milk. In sheep and goats, the principal causative organisms are *B. ovis* and *B. melitensis*, although goats can also be infected with *B. abortus*. In camels, there have been findings of *B. abortus* and *B. melitensis*, with camel milk possibly being a vehicle for human infections in Middle Eastern countries (Sprague et al., 2012). Further, investigations that target the seroprevalence of brucellosis have been on *B. abortus* in yaks (Zeng et al., 2017). A review of the recently isolated *B. melitensis* biovar 3 from cattle, buffaloes, humans and camels has implicated the bacterium's adaptability using modern biotyping techniques such as the Bruce-ladder assay. The fact that *B. melitensis* biovar 3 is versatile confirms the ability of this bacterium to thrive among various species (Sayour et al., 2020). *B. abortus* from apparently healthy female dogs and cats in cattle farms revealed their possibility of becoming asymptomatic carriers for the transmission of bovine brucellosis (Wareth et al., 2014). The results indicated that companion animals could not be ruled out from brucellosis monitoring and control policies.

Transmission:

Brucella is an important pathogen to human and animal health; however, it has several ways of transmission that complicate the control measures. In animals, *Brucella* concentrates and reproduces in the uterus, more so in aborted foetuses, placental tissues and uterine secretions. Nursing young ones get infected by contaminated milk and the bacteria can survive for a long period in cool and wet surroundings. Common sources of infection in animals involve contaminated feed and water and reproductive materials like foetuses and uterine discharges. Inhalation of the bacteria and contagion through natural service or artificial insemination from infected bulls are other chief modes of transmission. Contact with infected animals, especially when cattle lick aborted foetuses or newly born calves that have a heavy bacterial colonization, substantially increases disease transmission (CDC, 2017). Humans often acquire *Brucella* through raw milk and milk products, such as butter, cheese, ice cream and yogurt, or by consuming contaminated vegetables and under-cooked meat. Brucellosis is a severe occupational hazard among people involved in animal handling, food preparation and laboratory research. Examples of such individuals are dairy farmers, veterinarians, butchers and slaughterhouse workers, who come into contact with infected animals or materials, mostly through skin abrasions or inhalation of aerosols. *Brucella* cultures are also hazardous to laboratory workers where high rates of laboratory-acquired infections are reported (Bouza et al., 2005). The complicating factor in the transmission dynamics introduced by the presence of *Brucella* in wildlife is its ability to infect livestock and humans. The situation is thus complicated, underlining the need for increased education and strict adherence to safety among livestock handlers to effectively control the disease (Cutler et al., 2005; El-Wahab et al., 2019).

Distribution:

Brucellosis is a zoonosis with dynamic geographical distribution, as it represents both new outbreaks and re-emergences in areas that have previously experienced outbreaks. In some countries, such as Central Asia and the Middle East, brucellosis is rapidly increasing in humans, while in some countries, like Canada and Australia, cases of brucellosis are low or under very good control. On the contrary, acute brucellosis persists in Mediterranean Europe, Central and South America, Mexico, Africa, Central Asia, India and Italy (Dorneles et al., 2015). The World Animal Health Organization global report (from 1996 to 2014) categorizes 156 countries the status of brucellosis as: a) enzootic, countries that are infected or free for less than three years; b) non-enzootic, not detected within three years; or c) brucellosis-free, those countries in which it was absent throughout the study period. Brucellosis-free countries are mainly in Europe and Oceania, while enzootic areas include parts of Central and South America, Africa and Asia (Cardenas et al., 2019a). The infection, however, has been endemic in specific regions such as Western Asia, India, the Middle East, Southern Europe and South America (Mantur and Amarnath, 2008).

The etiology of brucellosis in different parts of Africa, South America, Brazil, Italy, Pakistan and Egypt is largely associated with *B. abortus* biovar 1 in the water buffalo population (Fosgate et al., 2002; Megid et al., 2010; Wareth et al., 2014; Ali et al., 2017). In Italy, the agent *B. abortus* induces the disease in both bovine and water buffaloes and its prevalence is particularly high in southern areas of the country (Garofolo et al., 2017). *B. abortus* biovar 3 is prevalent in Iran, while *B. abortus* biovar 1 causes various outbreaks among water buffalo populations in Africa and South America (McDermott and Arimi, 2002). Brucellosis is still recognized as an endemic disease in Egypt (Abdelbaset et al., 2018). *B. melitensis* infection in cattle was reported and it accounted for an important threat to countries like Kuwait, Saudi Arabia, Israel and some Southern European ones (Yilma et al., 2016). Epidemiology of the disease remains sporadic with new strains likely to emerge and adapt to new animal species and changing conditions (Caksen et al., 2002; Mantur et al., 2006).

Seroprevalence of 6.3% was reported for brucellosis in cows and buffaloes in Pakistan, it varied between the sampling sites, associated with factors such as stock replacement, species, sex, insemination methods and herd size (Ali et al., 2017). A countrywide meta-analysis of data in India indicated that brucellosis is significantly endemic, with an overall prevalence rate of 12% or less (Deka et al., 2018). On average, the national reports documented 5% in cattle, 3% in buffalo, 7.9% in sheep and 2.2% in goats, showing differences in the levels of the disease across species (Renukaradhya et al., 2002). In a study by Pathak et al. (2016), a total of 481 samples comprising milk, blood, vaginal swabs, vaginal discharges, placental tissue and foetal tissues were evaluated from 296 animals. The authors reported the positivity rate for brucellosis was 30.4% by RBPT and 41.6% by indirect ELISA. Studies from Punjab gave higher prevalence rates of 13.4%-16.4% in buffaloes and 9.9%-20.7% in cattle (Dhand et al., 2005). Recent studies on zoonotic diseases in North Eastern India have concluded that bovine brucellosis has affected nearly 17% of cattle in that region (Barman et al., 2020). A six-year bacteriological and genomics study on *B. abortus* in Meghalaya revealed an overall prevalence of 6.4% by RBPT and 10.7% by ELISA. Notably higher prevalence rates were observed in milk samples (17.5%) and blood samples (37.7%) when analyzed using direct PCR (Shakuntala et al., 2021).

Pathogenesis:

Gopalakrishnan et al. (2016) identified the key survival and virulence factors that Brucella requires for pathogenesis: LPS, urease, adenine monophosphate, guanine monophosphate, Vir B and a 24-kDa protein. Unlike most bacteria, Brucella does not carry any genes coding for plasmids, pili, exotoxins, or capsules that could contribute to its adhesive and invasive properties (Seleem et al., 2008). The bacteria infect the body via the ingestation or inhalation, or through damaged skin and further infect immune cells like macrophages and dendritic cells. *B. abortus* infects the placenta and mammary glands of pregnant animals during pregnancy, resulting in abortion, while in non-pregnant animals they continue to excrete the organism in their secretions (de Figueiredo et al., 2015). Normally they are isolated from milk, lymph nodes, spleen and the uterus, though some infections may spread to bones, joints, brain and eyes. In bulls, *B. abortus* affects genital organs and lymph nodes, with bacteria present in semen during acute and intermittently in chronic phases (Acha and Szyfers, 2001). Its ability to bypass immune defenses allows the pathogen to progress from an acute to a chronic infection, thus establishing long-term carrier states that vastly complicate control efforts (Amjadi et al., 2019). According to studies by Perin et al. (2017) in Brazil, Brucella infection down-regulates enzymes like adenosine deaminase and catalase in cows, hence leading to enhanced oxidative stress and possibly further inflammatory responses.

Clinical Signs:

In animal:

Brucellosis presents a variety of clinical signs across different animal species, predominantly affecting the reproductive system. The disease has an incubation period lasting from two weeks up to several months and infected calves most often stay asymptomatic until maturity. The most frequently reported symptoms are late-stage abortions, weak calves and decreased fertility resulting in retained foetal membranes and endometritis with reduced milk production (Abdisa, 2018). In infected herds, abortion rates range from 30 to 80% (Kiros et al., 2016). Fibrinous pleuritis and interstitial pneumonia are seen in newborn calves and aborted foetuses. Brucellosis in non-pregnant animals may evolve into the chronic phase, posing a problem to its diagnosis since antibodies often are no longer detectable in blood samples once they are released by B-1a cells after an initial immune response (OIE 2009). Symptoms of bovine orchitis, epididymitis or presence of hygroma (in chronic cases) can be seen in the bulls. The disease can also cause cervical bursitis in livestock (de Macedo et al., 2019).

In human:

Brucellosis is generally an acute or subacute febrile illness that includes symptoms such as intermittent or remittent fever, malaise, anorexia and prostration, occasionally with splenomegaly or hepatomegaly (Mantur et al., 2006). Untreated, the illness may continue to progress over weeks or months, making it difficult to diagnose because of its similarity to a wide range of other infections. Infection may lead to pathologic involvement of various organs and tissues, which presents as arthritis, spondylitis, sacroiliitis, osteomyelitis and bursitis, which may occur with minimal or no fever at all. Neurologically, there can be meningitis and brain abscesses, while ophthalmologically, it presents with uveitis and optic neuritis (Tikare et al., 2008). On the other hand, brucellosis can also cause anemia, thrombocytopenia, nephritis, cardiovascular effects such as vasculitis and endocarditis, respiratory effects like bronchopneumonia and gastrointestinal effects like peritonitis and pancreatitis. There exists the risk of spontaneous abortion in pregnant women, more so during the first or second trimester of pregnancy (Yang et al., 2018). Human-to-human transmission is very rare but might occur due to sexual contact or from mother to neonate (Kato et al., 2007). Asymptomatic carriers pose a major problem in diagnosis and control, as depicted in several studies reporting a remarkable prevalence of Brucella antibodies (10%) among asymptomatic field workers in Sudan (Osman et al., 2015).

Pathology:

In animals, Brucella infections normally lead to granulomatous inflammatory lesions in lymphoid tissues and other organs, with systemic dissemination at the generalized stage of infection. Brucella organisms are disseminated in all body tissues and tend to localize in reproductive tissue, causing abortion in females and infertility in males. The organism metabolises erythritol, which helps in their survival and proliferation in trophoblast cells (Anderson and Smith, 1965). This results in necrotic placentitis, due to invasion of the uterus by the *Brucella* and this may be either localized or generalized and in severe forms causes early foetal death and abortion, or in its sub-acute or chronic form, late-term abortion or the birth of live but infected calves. The affected cotyledons are often enlarged, congested and covered with sticky yellowish or brownish exudates. The areas between the cotyledons swell and turn opaque, losing their homogeneous red colour. Most of the time, their livers and spleens are enlarged, showing considerable abdominal fluid, they are mostly hairless, fully developed and usually lung infiltration results in bronchopneumonia. In some instances, the infiltration by the cellular element in the bronchioles and the paraphysium leads to sandy cobblestone-like lesions characteristic in almost a pathognomonic lesion for brucellosis (Stableforth and Galloway, 1959).

Diagnosis:

Brucellosis is an important disease with grave therapeutic and infection control implications, where early and accurate diagnosis is imperative. The precise clinical diagnosis of the disease requires several key features of epidemiology and historical background. Diagnostic tools such as bacterial culture techniques and serological assays for brucellosis detection in individual animals and screening of herds play a very critical role in surveillance programs and strategic planning of management and eradication efforts worldwide.

Different Tests	Name of Tests	Description	References
Gold standard test	Isolation and Identification	Infected animals are a good source of isolation and among them, uterine discharges and aborted fetuses are the best. From aborted fetuses, samples of choice are stomach contents, spleen, liver, lungs and lymph nodes. Biosafety level III laboratory is necessary for handing infected samples. *Brucella* medium base, tryptose (or trypticase)–soy agar (TSA) is the commercially available dehydrated basal medium. For cultures such as *B. abortus* biovar 2, 2–5 percent bovine or equine serum needs to be added for its growth. Blood agar base or Columbia agar gives excellent results. Serum–dextrose agar medium or glycerol dextrose agar are other media that give good results and help in the observation of the morphology of the colony.	Radostits et al., 2000
Herd screening test	Milk Ring Test	Periodically dairy herds should be screened with abortus bang ring test on pooled milk sample.	Quinn et al., 1994
Serological tests	Rose Bengal Plate Test (RBPT)	RBPT is a rapid screening test for individual animals. The sensitivity of RBPT is very high, but it is less specific.	Mantur et al., 2006
	Complement Fixation Test (CFT)	The complement fixation test (CFT) is a very specific test that can detect IgM and IgG antibodies.	
	Standard tube Agglutination Test (SAT)	SAT is the most popular diagnostic tool used worldwide for the diagnosis of brucellosis due to its simplicity and economy. SAT accounts for aggregated quantity of IgM and IgG, while the quantity of specific IgG is measured by 2-mercaptoethanol (2ME) treatment of serum sample.	Almuneef and Memish, 2002
	Brucellin test	It measures delayed type hypersensitivity reaction evident from increased thickness of skin. This test is especially useful as a confirmatory test in unvaccinated animals and	OIE, 2009

		is an alternative immunological test as per OIE.	
	Enzyme-linked Immunosorbent Assay (ELISA)	Indirect ELISA measures IgG, IgM and IgA levels in serum, which is useful in clinical diagnosis of brucellosis. Indirect ELISA has higher sensitivity and specificity as compared to SAT.	Al-Shamahy and Wright, 1998
Molecular technique	Polymerase Chain Reaction (PCR) assay	PCR is a rapid diagnostic method, which may be applied even on samples of poor quality. This could be used for epidemiological interpretations and analysis as well as for molecular characterization. A number of sequences have been recognized as targets for genus-specific PCR assays for confirmation of *Brucella species*, viz., omp2 and bcsp31,16S rRNA and the 16S-23S region. Bruce-ladder multiplex PCR assay developed for rapid identification of *Brucella* spp.	Habtamu et al., 2013
Newer tools and modifications		Several field level tests, viz., lateral flow assay (LFA) and latex agglutination developed recently are easy to use and quick. Loop-mediated isothermal amplification (LAMP) of DNA, as well as real-time PCR, have been proven as significant, sensitive, quick and specific diagnostics for *B. abortus* and other *Brucella* spp.	Mizanbayeva et al., 2009; Karthik et al., 2014

Prevention and Control:

The increase in global trade of animal products accelerates the spread of *Brucella* pathogens. Therefore, the need for close conformity to international standards regarding animal testing and quarantine, like the OIE International Zoo-Sanitary Code or the regional regulations, is strongly insisted (OIE 2016). While test-and-slaughter is a common measure across most South East Asian countries, making a diagnosis and tracing animal movement are serious complications to stamping out infection (Zamri-Saad and Kamarudin, 2016). This is further hindered because farmers are often unaware and prefer treating with antibiotics rather than searching for root cause of infection in its reservoirs (Hull and Schumaker, 2018). Effective control of animal brucellosis requires a reliable surveillance system, prevention against disease occurrence, source elimination of the *Brucella* and prevention of its reintroduction into the herd. A significant number of the meaningful strategies for control include certifying all the new animals, following the vaccination policies that have been set and ensuring the use of brucellosis-free semen (Cardenas et al., 2019b). The consumption of raw milk remains a health risk in endemic regions; therefore, pasteurization and good hygiene practices are of paramount importance (Dadar et al., 2019a; 2019b). Vaccination with strains like *B. abortus* S19 and RB51 forms an important part in the control of bovine brucellosis (Tabynov et al., 2015). Long-term strategies, including the 20-year vaccination program in India, has been undertaken that shown some very promising results in terms of reducing infection rates (Singh et al., 2018). Active surveillance is necessary to prevent and control disease in small farms, with focused education among farmers and veterinarians about possible zoonotic transmission (Ryu et al., 2019).

Conclusion:

Brucellosis continues to be among the greatest priorities to public health globally, whose control is pegged on effective collaboration between the veterinary and public health sectors. Budgetary constraints, lack of services for sick animals and grossly inadequate monitoring and surveillance are some of the barriers to brucellosis management. The extensive and well-financed monitoring and surveillance programs in endemic areas of the disease can circumvent such barriers. Animal registration and identification, access to quality veterinary and medical services and appropriate compensation mechanisms are key components of a successful control strategy. This requires an integrated approach that brings together financial investments by the government, semi-government organizations, the private sector and farmers to ensure sustainability in disease control.

Conflict of interest:

The author declares that no conflict of interest exists.

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***Corresponding author's email ID:** koushikkakoty43@gamil.com

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