Global Veterinaria 25 (3): 106-117, 2023
ISSN 1992-6197

DOI: 10.5829/idosi.gv.2023.106.117

Review on Epidemiology, Economic and Public Health Importance of Bovine Brucellosis

Teshale Adere Senbeta, Wondimagegn Demissie Guchito and Mebratu Meles Asfaw

Department of Livestock and Fisheries, Veterinary Teppi, Sheka Zone, Yeki Woreda, Ethiopia

Abstract: Brucellosis is a highly contagious, zoonotic and economically important bacterial disease of animals worldwide. The disease in cattle, usually caused by *Brucella abortus*.It occasionally caused by *Brucella melitensis* or *Brucella suis*. It is characterized by late term abortion, infertility, retained placenta, secondary endometritis and reduced milk production with the excretion of the organisms in uterine discharges and milk. Full-term calves may die soon after birth. The disease is transmitted to susceptible animals by ingestion of contaminated feed and water, contact with aborted fetuses, fetal membrane, uterine discharges and via inhalation. In animals, the concentration of the bacteria is the highest in pregnant uterus. The aborted fetus, placental membranes, fetal fluids and other uterine discharges are the major source of infection. The clinical signs, manifestations and multiple complications in brucellosis in different animal species are firstly related to the reproductive tract. In Humans, the main presentations are acute febrile illness, with or without signs of localization and chronic infection. Treatment of infected livestock is not attempted because of the high treatment failure rate and costs and the potential problems related to maintaining infected animals in the face of ongoing eradication programs. The control of brucellosis in ruminants is the key to preventing the disease in humans and can best be achieved through a combination of livestock vaccination, removal of infected animals and improved hygiene practices that minimize the risk of introducing infection to disease-free flocks/herds. The distribution of brucellosis in different geographies is highly dynamic, with emergence of new areas of infection and re-emergence of infection in areas where infection existed earlier. In Ethiopia studies in many parts by different persons on the prevalence of brucellosis ranges from 0.5 % - 11.2%. Thus, awareness creation for the society about public and economic significances of the disease is essential in reducing burden of the disease as well as One Health approach can aid in control of this disease, both in animals and man.

Key words: Cattle · Brucella · Human · Abortion · Economic Significance And Zoonosis

INTRODUCTION

The Food and Agriculture Organization (FAO), the World Health Organization (WHO) and the Office International des Epizooties (OIE) all rank brucellosis as one of the most common zoonoses in the world due to its high contagiousness, zoonotic transmission and economic importance [1]. In cattle, the disease is typically brought on by Brucella abortus, though it can also be brought on by *Brucella melitensis* and *Brucella suis*. It is characterized by late-term abortion, infertility and decreased milk production due to retained placentas, secondary endometritis and the excretion of the organisms in uterine discharges and milk. The birth of a full-term calf could result in death. Abortion rates in herds that are entirely vulnerable might range from 30-80% [2]. Animal brucellosis causes direct socio-economic effects in communities who depend on animal production for their livelihood [3]. Losses in animals are attributed to direct effects on their offspring due to abortion, stillbirth and infertility whereas indirect losses are due to reduction in milk yields and humans suffering resulting from the disease [4, 5].

The most common names for brucellosis in humans are undulant fever, Crimean fever, Mediterranean fever, remitting fever, Maltese fever, goat fever and Gibraltar fever, whereas the names for the disease in cattle include contagious abortion or Bang's disease [6]. To paraphrase the Bruce, they were a species of bacterium and their hosts were the pens [7]. Small ruminants serve as the

Corresponding Author: Wondimagegn Demissie Guchito, Department of Livestock and Fisheries, Veterinary Teppi, Sheka Zone, Yeki Woreda, Ethiopia.

major hosts for *B. melitensis* and cattle serve as the overflow host, increasing the risk of brucellosis in mixed farming of cows, buffaloes, sheep and goats [8].

Due to several difficulties with diagnosis, reporting and inadequate to nonexistent surveillance systems, particularly in malaria endemic areas with variances based on pastoral systems, the prevalence of animal and human brucellosis is typically unknown in LMICs [9]. Although the disease is highly prevalent and varies from country to country, there is generally poor disease surveillance. Variations in prevalence are thought to be caused by factors such as buying infected cattle from the market for replacement or upgrading, the nature of animal production, sharing of bulls, use of open-range grazing, demographic factors, regulatory concerns and interactions between climate and wildlife [10]. Numerous publications have used serology to demonstrate the presence of brucellosis in Ethiopian cattle. While most studies revealed that cattle raised in crop-livestock mixed farming had a low seroprevalence (below 5%), a high seroprevalence of brucellosis (22%) has been found in the dairy herd of Cheffa State Farm [11-13]. The status of cattle brucellosis in pastoral parts of the nation, where a sizable population of cattle is raised, is poorly documented in published literature. In contrast to the agropastoral system, a study conducted so far in Ethiopia's east Showa zone revealed a substantially higher seroprevalence [14].

The effects of brucellosis in animals include abortion, mortality, decreased milk and meat output and decreased reproductive effectiveness [15]. The costs of treating illnesses like brucellosis in animals are typically astronomically high [16]. In spite of the losses and yield reductions, the disease is not very noticeable in its chronic form; hence its causes are frequently overlooked. Particularly in tropical locations, its detrimental impact on the cost-effectiveness of livestock production is grossly underappreciated under the current system of extensive management [17]. Brucellosis illness to the herds reduces livestock production and reproduction performance evident by frequent episodes of abortion especially during the last trimester, retention of placenta, metritis, birth of weak calves, infertility in bulls and cows and 20% reduction in milk production from infected cows [18-20].

Effective control tactics for this illness include surveillance, transmission prevention and culling as a means of reducing the infection reservoir [21-22]. By following stringent immunization protocols, some nations have successfully reduced Brucella infection to some extent. These protocols include the use of suitable smooth live vaccines, reliable diagnostic tools, mass immunization of large populations and regular culling of Brucella-positive animals. In the lack of competent immunological animals, sickness may worsen due to increased virulence, host jumping and wider transmission in several species if thorough immunization and precise diagnosis are not carried out [7].

In highly endemic locations, vaccination of animals is advised. Effective attenuated vaccines against B. abortus infection include B. abortus strains 19 and RB51 [23]. When domestic animals were raised in close proximity to their owners and handlers in the past, any flaw in animal management and consumption of unclean dairy or other animal products were key contributors to the spread of bovine brucellosis and its zoonotic form in humans. Along with domestication, anthropogenic adaption of wild animals caused this virus to expand its host range and hop from one host to another, possibly transmitting between different species. With the passage of time, brucellosis has become a disease causing serious economic losses, which is capable of affecting many species of animals as well as humans owing to the genetic adaptation of the pathogen against a variety of immune defense mechanisms of different hosts. However, humans act as dead-end host and brucellosis occurs with more severe clinical manifestation in man [7]. Around 50,000 human cases of brucellosis were reported each year globally, taking into account the disease's ability to spread from humans to animals [24]. Dairy products that are unpasteurized, inadequately pasteurized, or raw and that come into touch with contaminated tissues or secretions are the primary routes of transmission to humans [7]. Due to the high incidence of treatment failure, the high expense and probable issues associated with retaining diseased animals in the face of ongoing eradication attempts, treatment of infected cattle is not tried [25]. As a result, the goals of this seminar paper are to: describe the present epidemiological aspects of Brucellosis and the importance of Bovine Brucellosis for Public Health; to briefly highlight the Economic Importance of Bovine Brucellosis.

Etiology: There are no capsules, endospores, or native plasmids in the facultative intracellular, gram-negative, non-spore-forming, partially acid-fast and non-capsulated Brucella species. While Brucella is resistant to freezing and thawing, most disinfectants that are effective against gram-negative bacteria will kill it. Brucella in milk is effectively eliminated by pasteurization. The bacterium has a diameter of 0.5-0.7 and a length of 0.6-1.5. They are positive for oxidase, catalase and urease. Despite being classified as non-motile, Brucella species possess all the genes needed to put together a functional flagellum, with the exception of the chemotactic system [26]. Proteobacteria's division a-2 includes Brucellae [27]. A total of six classical and seven novels *Brucella* species have been recognized from a wide spectrum of susceptible hosts. Species affecting terrestrial animals are seven in number including *B. abortus, B. melitensis, B. suis, B. ovis, B. canis, B. neotomae and B. microti* [28].

The two other species, *B. ceti* and *B. pinnipedialis* affect marine mammals [29]. *B. papionis* isolated from baboons and *B. vulpis* from red foxes were also added to the list of genus *Brucella* [30]. Moreover, seven biovars have been recognized for *B. abortus*, three for *B. melitensis* and five for *B. suis*. Rest of the species has not been characterized into biovars. The *Brucella* nomenclature is based on the principal host species. Reports also document the isolation of 36 atypical *Brucella s*pp. from frogs [30, 31].

Epidemiology

Geographical Distribution: The geographic distribution of brucellosis is very dynamic, with both the formation of new foci of infection and the resurgence of infection in previously infected areas. There are now more places where human brucellosis is prevalent in Central Asian and Middle Eastern nations, where prevalence is steadily rising [24].Except for Canada, Australia, Cyprus, Norway, Finland, the Netherlands, Denmark, Sweden, New Zealand and the United Kingdom, this disease is widespread throughout the world. However, there is a significant brucellosis prevalence in Mediterranean Europe, Central and South America, Mexico, Africa, Near Eastern countries, Central Asia, India and Italy. Many nations have reporting and notification requirements for brucellosis, however there is an obvious issue with the disease's systematically low reporting rates [32].

According to the prevalence of brucellosis in animals, 156 nations were divided into three groups in a report by the World Organization for Animal Health (OIE) that covered the period of 19 years (1996-2014). These are the three groups: non-enzootic for brucellosis: although brucellosis may be present, countries in this category are free of disease for a period of 3 years; enzootic for brucellosis: countries that are infected or free of brucellosis for less than 3 years; and free of brucellosis: countries that were free of brucellosis throughout the study period of 19 years. Europe and Oceania are home to disease-free nations, while Africa, Central and South America and some regions of Asia are home to enzootic nations with significant disease prevalence [33].

Brucellosis is endemic in Western Asia, India, Middle East, Southern Europe and South America [34, 35]. Study in Iran reported that *B. abortus* biovar 3 is the most prevalent biovar [36]. Reports of low incidence of brucellosis in endemic areas could be due to either inadequate surveillance or under reporting [37]. Brucellosis is mainly caused by *B. abortus* biovar 1 in water buffaloes in parts of Africa, South America, Brazil, Italy, Pakistan and Egypt [38]. In Italy, cattle and water buffalos both are affected by *B. abortus* mainly in southern areas. In Egypt, brucellosis is not endemic problem and is usually crosses it from the southern countries with the importation of camels [39].

Reports of *B. melitensis* infection in cattle are pouring which is a major threat in Kuwait, Saudi Arabia, Israel and some southern European countries [40]. The epidemiology of this disease remains dynamic and unpredictable as several new strains could emerge and present strains could adapt to new animal species as well as changing situations. Disease is rare in children but in endemic areas, such cases have been reported [41-42]. Comprehensive reports on the studies from different continents are summarized in the following section.

Host Range and Brucella Diversity: B. abortus is the main strain that infects cattle. When cattle share pasture or facilities with diseased pigs, goats, or sheep, they may also become momentarily infected with B. suis and more frequently with B. melitensis. Cow's milk can transmit B. melitensis and B. suis, posing a major risk to the public's health [43]. B. melitensis is the primary causative agent of brucellosis in goats. Goats can contract B. abortus infection in some locations, like Brazil, where B. melitensis is not present [44]. When camels are pastured with sick sheep, goats and cattle, they may contract B. abortus and B. melitensis. Milk from infected camels represents a major source of infection that is underestimated in the Middle East [45].The main etiologic agent for dog brucellosis is *B. canis*, but sporadic cases of brucellosis in dogs caused by *B.abortus*, *B. suis* and *B. melitensis* have been reported [43]. Nine *Brucella* species are currently recognized, seven of them that affect terrestrial animals are: *B. abortus, B. melitensis, B. suis, B. ovis, B. canis, B. neotomae and B. microti* [28] and two that affect marine mammals are: *B. ceti and B. pinnipedialis* [29-44]. The first three species are called classical *Brucella* and within these species, seven biovars are recognized for *B. abortus*, three for *B. melitensis* and five for *B. suis*. The remaining species have not been differentiated in to biovars. The strains of Brucella were named based on the host animal preferentially infected [46].

Source of Infection and Mode of Transmission

In Human: Consumption of dairy products, particularly raw milk, soft cheese, butter and ice cream, is the main cause of infection in people. Though the bacterial load is very low, it is nevertheless possible for uncooked animal muscle or tissue to be consumed, as well as raw vegetables and water contaminated by feces [47]. In enzootic environments, transmission by contact predominates. Man, contracts Brucella through handling contaminated animal tissues and by coming into close contact with other infected materials. Skin abrasions or unbroken skin may allow Brucella to enter the body and there is also evidence of airborne and trans-conjunctival transmission. As a result, stockyard, slaughterhouse, butcher and veterinary staff are susceptible to human brucellosis [48].

In Animal: In animals, the concentration of the bacteria is highest in pregnant uterus. The aborted fetus, placental membranes or fluids and other uterine discharges are considered as major source of infection. Infected animals also shade organisms in milk which serve as source of infection for the new born. Contaminated feed can spread the infection from infected pasture over long distance during purchasing and selling activities. The disease is transmitted to susceptible animals by ingestion of contaminated feed and water, contact with aborted fetuses, fetal membrane and uterine discharges; infection by inhalation is also possible. The use of infected bull for artificial insemination also poses an important risk and spreads the infection to many herds [49].

Risk Factors

Host Risk Factors: Susceptibility of cattle to *B. abortus* infection is influenced by the age, sex and reproductive status of the individual animal. Sexually mature pregnant cattle are more susceptible to infection with the organism than sexually immature cattle of either sex. Susceptibility increases as stage of gestation increases [50].

Pathogen Risk Factors: *B. abortus* is a facultative intracellular organism capable of multiplication and survival within the host phagosome. The organisms are phagocytized by polymorphonuclar leucocytes in which some survive and multiply. The organism is able to survive within macrophages because; it has the ability to survive phagolysosome [51]. The bacterium possesses an unconvenential non-endotoxin lipopolysaccharide, which confers resistance to antimicrobial attacks and modulates the host immune response. These properties make lipopolysaccharide an important virulence factor for *Brucella* survival and replication in the host [52].

Management Risk Factors: The spread of the disease from one herd to the other and from one area to another is almost always due to the movement of an infected animal from infected herd in to a non-infected susceptible herd. A case-control study of brucellosis in Canada indicates that, herds located close to other infected herds and those herds whose owners made frequent purchase of cattle had an increased risk of acquiring brucellosis. Once infected, the time required to become free of brucellosis was increased by large herd size, active abortion and by loss housing [52].

Occupational Risk Factors: Laboratory workers handling *Brucella* cultures are at high risk of acquiring brucellosis trough accidents, aerosolization and/or inadequate laboratory procedures. In addition to this, abattoir workers, farmers and veterinarians are at high risk of acquiring the infection [51].

Pathogenesis: Numerous virulence factors, host defense system evasion mechanisms and Brucella's manner of intracellular survival have all been thoroughly reviewed [53]. Factors including LPS, urease, adenine monophosphate, guanine monophosphate, vir B and 24-kDa protein are the main pathogenic components of brucellosis. The Brucella genome lacks the traditional virulence genes that produce plasmids, pili, exotoxins and capsules [54]. Transmission routes include ingestion, inhalation, conjunctival contact and cutaneous abrasions or wounds. When B. abortus enters the host body, it multiplies in the intracellular environment of phagocytic cells like macrophages and dendritic cells. When a woman becomes pregnant, the bacteria circulate to the trophoblasts and the mammary gland and then extremely expansively expand to cause abortion. While, in non-pregnant animals, bacteria continue to multiply and shed in environment through various body secretions and excretions [7, 55].

Brucella is frequently isolated from milk, spleen, iliac lymph nodes, supra-mammary lymph nodes and uterus. However, infections can also spread to the brain, eyes, bones and joints. Bulls' sexual organs and related lymph nodes are the usual places where the germs are isolated. In the early acute phase, a considerable number of bacteria are expelled in semen, but later in the chronic phase, the excretion gradually diminishes. Bacterial excretion may occur periodically or continuously over a long period of time [49]. In females, Brucella enters the placenta by the hematogenous pathway and then travels to the fetus. The uterus and reproductive tract of pregnant females is the site of the bacterial preference because allantoic fluid components in females promote

Brucella development. The elevated level of erythritol in the placenta and fetal fluid from fifth month of gestation is thought to be an important factor for abortion in animal. Erythrophagocytosis by trophoblasts localized in the placentome in vicinity of chorioallantoic membrane resulting in rupture of cells and ulcer formation in the chorioallantoic membrane. Abortion occurs due to the damage inflicted by the bacteria on the placenta and also due to stress induced hormonal changes [47].

Some author analyzed the changes in adenosine deaminase activity and the oxidative stress in brucellosis serologically positive cows in Brazil. It was revealed that there was reduction in the activity of adenosine deaminase as well as catalase in serologically positive animals; simultaneously, an increase in the level of oxidative stress markers along with superoxide dismutase as well as thiobarbituric acid reactive substances was observed in *B. abortus* infected cows. A reduction of adenosine deaminase along with oxidative stress could possibly be related to inflammatory response modulation [56]. As *Brucella* spp., is intracellular pathogens which can survive within the phagocytic cells by using various escape strategies to undermine the host immune defense mechanism, it can progress from acute to chronic and to carrier form in host. Studies have confirmed the role of gene polymorphisms [57].

Clinical Signs

Clinical Signs in Animals: The predominant symptom of B. abortus infection in infected animals is reproductive failure, manifested by abortion and the birth of weak progeny that continue to be carriers in the herd. The reproductive system is first and foremost associated to the clinical indications, manifestations and numerous consequences of brucellosis in diverse animal species. The incubation phase might last anywhere between two weeks and several months. Calves may be infected at an early stage, but symptoms won't appear until they are fully developed. Accordingly, it shows up as late abortions in pregnant animals, the birth of weak calves, decreased fertility, the retention of fetal membranes, endometritis and a decrease in milk production [58]. In sensitive herds, the abortion rate might range from 30 to 80% [59]. Full-term calves may pass away quite quickly after giving birth. Both newborn calves and aborted fetuses can develop fibrous pleuritis and interstitial pneumonia [60]. Orchitis and epididymitis are two clinical signs that appear in male animals, whereas hygroma is a sign of chronic illnesses [61]. Cattle cervical bursitis caused by brucellosis has also been documented. The initial inflammatory phase in the seminal vesicles is followed by a chronic stage with significant fibrinoid induration. Dry necrosis areas form, become encased by fibrinous tissue and finally compress, frequently shrinking the testicles below normal size. In some cases, it may soften with the production of a soft fluctuating lesion containing thin purulent exudate [62].

In highly susceptible non vaccinated pregnant cow, abortion occurs after the 5th months of pregnancy; in bull, orchitis and epididymitis are cardinal signs. In case of horse, it is usually associated *B. abortus* with chronic bursal enlargement of the neck and withers and abortion in mares. Brucellosis in swine has acute symptoms like abortion, infertility and birth of weak piglets, orchitis, epididymitis and arthritis. Sheep and goats have similar to that observed in other species of animals [62].

Abortion in goats occurs most frequently in the third or fourth months of pregnancy. In case of dog and cats, infertility either in male or female, abortion and still birth or weak puppies are common manifestations. Infected livestock exhibit clinical signs of great economic significance to small and large scales livestock farmers and industries. Characteristic but not specific signs of brucellosis in most animal hosts are abortion or premature births and retained placenta. Interference with fertility is usually temporary, most infected animals will abort only once and some are unaffected [39].

In sexually mature animals the infection localizes in the reproductive system and typically produces placentitis followed by abortion in the pregnant female, usually during the last third of pregnancy [33]. Other signs can include arthritis in cows and pig's splenic abscesses and small intestinal adhesions on post-mortem examination in sows orchitis or epididymitis in the case of *B. melitensis* and *B. ovis* in sheep [34]. Mastitis and lameness in goats and oozing skin lesions in horses(fistulous withers) Additionally, it can induce a substantial decline in milk production over an animal's lifespan, often udder is permanently infected, especially in cows and goats, with continuous shedding of the organism in milk [35]. Clinical signs of brucellosis in camels appear to be very rare [40]. In addition, clinical signs are not pathognomonic and diagnosis is dependent upon demonstration of the presence of *Brucella* spp. either by isolation of the bacteria or detection of their antigens or genetic material, or by demonstration of specific antibody or cell-mediated immune responses [41].

Clinical Signs in Humans: In Humans, the main presentations are acute febrile illness, with or without signs of localization and chronic infection. Range of non-specific clinical signs may be observed including malaise, fatigue, sweats, anorexia, headache, depression, abdominal or back the main presentations are acute febrile illness, with or without signs of localization and chronic infection [41]. Range of non-specific clinical signs may be observed including malaise, fatigue, sweats, anorexia, headache, depression, abdominal or back the main presentations are acute febrile illness, with or without signs of localization and chronic infection. Range of non-specific clinical signs may be observed including malaise, fatigue, sweats, anorexia, headache, depression, abdominal or back pain, arthritis, inconstant and prolonged fever, miscarriage. The fever of brucellosis may mimic that of enteric fever and an undulant fever pattern is seen in chronic infections. Fever may be absent among patients with end-stage renal disease who acquire brucellosis [42]. Mild lymphadenopathy is seen in 10 to 20% of patients; and splenomegaly or hepatomegaly in 20 to 30%. Hepatosplenic abscesses are visualized through imaging in 1.2% of cases and rare instances of splenic rupture have been reported. Bone and joint infections are common, including a high rate of vertebral osteomyelitis instances of acute or sternotomy infection, granulomatous myositis, bursitis and soft tissue or muscular abscesses. Most cases of *Brucella* monoarthritis represent reactive rather than septic disease Infection of natural or prosthetic joints (24 cases reported to 2016) and soft tissue. Subclinical sacroiliitis is common. Asymptomatic infection has also been reported [38]. Clinical and laboratory features vary widely. Endocarditis is well documented including isolated case reports of *Brucella* infection of prosthetic valves and devices such as implantable defibrillators and pacemaker leads. Rare instances of aortitis venous or arterial thrombosis, myocarditis and pericarditis have been reported [63].

Diagnosis

Bacteriological Methods: Specimen of fetal stomach, lung, liver, placenta, cotyledon and vaginal discharges are stained with Gram stain and modified Ziehl Neelsen stains. *Brucella* appears as small red-colored, coccobacilli in clumps. Blood or bone marrow samples can be taken cultured in 5-10% blood agar is used. To check up bacterial and fungal contamination; *Brucella* selective media are often used. The selective media are nutritive media, blood agar based with 5% sera-negative equine or bovine serum. On primary isolation it usually requires the addition of 5 -10% carbon dioxide and takes 3-5 days' incubation at 37°Cfor visible colonies to appear [17].

There are a range of commercially available culture media for growing *Brucella;* the most common basal media in use are triptcase soy, bacto tryptose, triptic soy and tryptone soya. Frequently, field samples are contaminated with other bacteria, thus, selective media should be used to avoid overgrowth by fast growing agents. The use of selective culture media is needed to increase the probability of success of bacterial culture and it is compulsory for the adequate bacteriological diagnosis of brucellosis. Any basal media mentioned above with agar may be used to prepare selective media. The most widely selective media used are the kuzdas, morse and farrell´s mediums [27, 64].

Serological Methods

Rose Bengal Plate Test: The RBT is one of a group of tests known as the buffered *Brucella* antigen tests which rely on the principle that the ability of IgM antibodies to bind to antigen is markedly reduced at a low pH. The RBT is a simple spot agglutination test where drops of stained antigen and serum are mixed on a plate and any resulting agglutination signifies a positive reaction. The test is an excellent screening test but may be oversensitive for diagnosis in individual animals, particularly vaccinated ones [61].

Complement Fixation Test: The sensitivity and specificity of the CFT is good, but it is a complex method to perform requiring good laboratory facilities and trained staff. If these are available and the test is carried out regularly with good attention to quality assurance, then it can be very satisfactory. It is essential to titrate each serum sample because of the occurrence of the prozone phenomenon whereby low dilutions of some sera from infected animals do not fix complement. This is due to the presence of high levels of non-complement fixing antibody isotypes competing for binding to the antigen. At higher dilutions these are diluted out and complement is fixed. Such positive samples will be missed if they are only screened at a single dilution. In other cases, contaminating bacteria or other factors in serum samples fix or destroy complement causing a positive reaction in the test, even in the absence of antigen. Such "anti-complementary" reactions make the test void and a CFT result cannot be obtained [61].

Treatment: As a general rule, treatment of infected livestock is not attempted because of the high treatment failure rate, cost and potential problems related to maintaining infected animals in the face of ongoing eradication programs [25]. Even though the complex nature of brucellosis makes it difficult to treat, long-term treatment with an antibiotic is thought to be beneficial. In most cases, antibiotics in combination are found to be more effective against the infection, however, the state of the disease still does not lose its importance [65, 66]. Several conventional antibiotics including tetracycline, trimethoprim - sulfamethoxazole, amino-glycosides, rifampicin, quinolones, chloramphenicol, doxycycline and streptomycin are commonly used in clinics [67]. Humans are treated with antibiotics (doxycycline with rifamipicine). Relapses are, however, possible [68]. However, rifampicin monotherapy is in common practice for treating brucellosis in pregnant women and combined therapy of sulphamethoxazole and trimethoprim is recommended for children [69].

Control and Prevention: Control of brucellosis in ruminants is the key to preventing the disease in humans and can best be achieved through a combination of livestock vaccination, removal of infected animals and improved hygiene practices that minimize the risk of introducing infection to disease-free flocks/herds [70]. Brucellosis is an infectious disease which has been controlled and eradicated in some countries in the world [71] in sub-Saharan Africa, animal health services delivered by the public sector have greatly decreased over the last 20 years due to various factors such as decreasing government budgets, particularly for operational costs of disease control. Thus, programs that require coordinated surveillance, information exchange and application of control measure are not implemented in many sub-Saharan countries [37].

In endemic areas, control of brucellosis is the first challenge. The only way to control human brucellosis is to control the animal disease and stop passage to man. Brucellosis has been controlled or even eradicated in a small number of wealthy countries, by long and costly programs of animal vaccination followed culling of infected animals at later stages. Food hygiene, especially pasteurization of milk is of great importance to prevent human infections. Excellent reviews by Blasco discus this in detail. Control of a disease such as brucellosis requires a 'One Health' approach [72].

Vaccination: Vaccination programs need good vaccines [5] two live vaccines, *B. Melitensis* Rev. 1 and *B. abortus* S19 have been used over past decades with great success for, respectively, small ruminant and bovine brucellosis control programs throughout the world. The *B. melitensis* REV 1 vaccine is an attenuated strain of *B. melitensis* and an effective method to reduce the prevalence of brucellosis among whole flocks or flocks in low-income countries and/or endemic countries [73].

Test and Slaughter: Test and slaughtering of positive animals are only successful in reducing the incidence if the herd or flock prevalence is very low which is feasible only in developed world. The decision about slaughtering of test positive animals is made after regulatory, economic and prevalence factors are considered. In developing countries, the isolation of test positive animals is essential, especially during and after parturition since immediate slaughtering of test-positive animals is expensive and requires animal owner cooperation [74]. Furthermore, the application of test and slaughter policies works well only under reliable diagnostic tests to avoid unnecessary decision due to false positivity [75].

Public Health and Economic Importance

Economic Impact, Loss and Cost of Bovine Brucellosis: Bovine brucellosis causes huge losses to the dairy industry; however, there is a dearth of comprehensive economic studies. It is also observed that terms such as economic impact, loss and cost of brucellosis are used by some researchers loosely and interchangeably. Economic impact can include direct (reduced milk yield, increased mortality) and indirect (vaccination, culling) costs. Direct impacts may further be classified as visible (abortion, repeat breeding), invisible (lower fertility), additional costs (e.g. treatment, vaccination) and revenue forgone (e.g. distress selling) [76]. Loss may comprise only those parameters that reduce benefits (e.g. reduced milk yield, reduced weight gain, reduced fertility, increased replacement cost, increased mortality etc.) while cost would comprise amounts spent for treatment and control (e.g. biosecurity, vaccination, movement control, disease surveillance, research etc.) of the disease [76].

Most economic estimates have not taken into consideration the loss caused by distress selling, feeding and management loss of pregnant animals in the event of abortion, person-days loss for treating animals, cost of antiseptic and detergents, cost of transportation related to treatment, cost of diagnosis etc. Most studies extrapolate the economic figures based on limited epidemiological information and assumptions developed in the given country or elsewhere. Few studies that estimate the economic impact of the disease based on rigorous epidemiological data collected from a randomly selected population. Because of lack of uniformity in approach to measurement of economic impact/cost/ loss and the fact that these are highly context specific, the estimates have also varied widely. Other reported that an economic loss caused by brucellosis was mainly due to reduction in milk production followed by cost of treatment and loss of the aborted calf. It was further stated that there was an average loss of 231 liters and 177 liters of milk (10% of total lactation yield) in Brucella positive cows and buffalo cow respectively, causing an economic loss of around USD 40. The average costs of treatment following abortion, repeat breeding and retention of placenta of dairy cattle were estimated at USD 4, USD 5 and USD 7 respectively [77].

Public Health Importance: Brucellosis (especially *B. melitensis*), remains one of the most common zoonotic diseases worldwide with more than 50,000 human cases reported annually [78]. The significance of brucellosis as zoonotic disease has ever increased in recent times, due to the expansion of international commerce in animals and animal products, with increase urbanization, intensive farms and animal products, having nomadic animal husbandry [34]. Despite the advances made in surveillance and control, the prevalence of brucellosis is increasing in many developing countries due to various sanitary, socioeconomic and political factors [24]. Transport of brucellosis to humans occurs mainly through the consumption of unpasteurized dairy products especially raw milk, soft cheese, butter and ice cream, through direct contact with infected animal parts (such as the placenta by inoculation through ruptures of skin and mucous membranes) and through the inhalation of infected aerosolized particles. Brucellosis is an occupational disease in shepherds, abattoir workers, veterinarians, dairy-industry professionals and personnel in microbiologic laboratories.

However, consumption of hard cheese, yogurt and sour milk are less hazardous, since both propionic and lactic fermentation takes place. Bacterial load in animal muscle tissues is low, but consumption of undercooked traditional delicacies such as liver and spleen has been implicated in human infection [47]. Air borne transmission of brucellosis has been studied in the context of using *Brucella* as a biologic weapon. In fact, *B. suis* was the first agent contemplated by the U.S. Army as a potential biologic weapon and is still considered in that category. In a hypothetical attack scenario, it was estimated that release of an aerosolized form of *Brucella* under optimal circumstances for dispersion would cause 82,500 cases of brucellosis and 413 fatalities. Cases of laboratory-acquired brucellosis are the perfect examples of airborne spreading of the disease [79]. Most common symptoms of brucellosis include undulant fever in which the temperature can vary from 37°C in the morning to 40°C in the afternoon; night sweats with peculiar odor, chills and weakness, insomnia, anorexia, headache, arthralgia, constipation, sexual impotence, nervousness and depression. Human brucellosis is also known for complications and involvement of internal organs and its symptoms can be very diverse depending on the site of infection and include encephalitis, meningitis, spondylitis, arthritis, endocarditis, orchitis and prostatitis. Spontaneous abortions, mostly in the first and second trimesters of pregnancy, are seen in pregnant women infected with *Brucella* [80].

CONCLUSION AND RECOMMENDATIONS

With the exception of those nations where bovine brucellosis has been eradicated, brucellosis continues to be one of the most prevalent zoonotic and animal illnesses in the globe. Due to hygienic, socioeconomic and political causes, brucellosis appears to be more widespread in emerging nations, especially in sub-Saharan countries like Ethiopia. The zoonotic illness brucellosis is very infectious and causes large reproductive losses in livestock. It is possible for humans to contract the disease directly from sick animals or animal carcasses, or by consuming tainted and unpasteurized milk and milk products. The two main clinical manifestations in humans are chronic infection and acute febrile sickness, with or without localization symptoms. Communities that depend on the production of animals for their livelihood are directly impacted by animal brucellosis on a socioeconomic level. Losses in animals are attributed to direct effects on their offspring due to abortion, stillbirth and infertility whereas indirect losses are due to reduction in milk yields and humans suffering resulting from the disease. The disease causes colossal economic losses globally in terms of reduced animal health and production and effect on public health, yet robust surveillance, prevention and control measures are lacking.

Based on the above conclusion, the following recommendations are forwarded as:

- ✓ In order to reduce the burden of the disease and use the One Health approach to help control it in both humans and animals, it is vital to educate society on the public and financial implications of the sickness.
- ✓ It is preferable to develop vaccines that offer defense against all Brucella species and biovars that cause bovine brucellosis.
- ✓ Implementation of a multidisciplinary, collaborative approach for efficient disease control and prevention as well as to reduce the financial losses and public health danger brought on by brucellosis.
- ✓ To restrict the dynamics of disease transmission between animal species and humans, proper attention for all animal species should be given in the research area. Due consideration should be taken around researches area for all animal species to limit the transmission dynamics of the disease in between animal species and humans.

✓ All researches related to the disease should be supported by the gold standard diagnostic approaches that empower us to currently the most wide distributed strains of Brucella agents both in humans and animal.

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