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Human and Animal Brucellosis: A Comprehensive Review of Biology, Pathogenesis, Epidemiology, Risk Factors, Clinical Signs, Laboratory Diagnosis, Public Health Significance, Economic Importance, Prevention and Control

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Abstract Brucellosis is a highly infectious anthropozoonotic disease caused by the bacterial genus *Brucella* and is prevalent throughout the world. It has a wide host range, and this makes brucellosis an important public health problem causing a negative impact on the economy of the affected country. The disease is endemic in the bovine population, resulting in an estimated economic loss of US dollars 344 billion to the livestock industry. Poor management, irrational animal movement, wide ranges of hosts, large herd size, and commingling of different animal species are risk factors for animal brucellosis. Globally, brucellosis is estimated to account for 500,000 cases in humans every year. The possible risk factors for human brucellosis are eating infected animal products, occupational exposure, and contact with diseased animals or their products and discharges. Human brucellosis is characterized by a variable incubation period and has many clinical manifestations. In humans, undulating fever is the most frequently observed clinical sign with infections reported during the early trimesters of pregnancy. The common measures of preventing animal brucellosis include proper hygiene, control of animal movement, and testing and slaughtering infected animals. Successful prevention of the disease can only be achieved when extension services emphasize addressing the impacts of risk factors for the occurrence of brucellosis. Generally, there is no single prevention strategy that inhibits the transmission of brucellosis amongst animals and humans. Therefore, public education on the transmission, source of infection, public health and economic importance of the disease needs to be undertaken. The control of human and animal brucellosis is multidisciplinary, requiring the efforts of all professionals, and farmers.

Keywords: *Brucella, brucellosis, diagnosis, control, economic importance, multidisciplinary approach, public health, Zoonosis*

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1. Introduction

Brucellosis is an economically important and widespread zoonotic infectious disease prevalent throughout the world. It affects a broad range of species of animals and humans, with an estimated half a million human cases reported annually worldwide [1,2,3]. It is an endemic disease in most of the developing world that causes a devastating loss to the livestock industry, especially small-scale livestock holders. The burden that the disease places specifically on low income countries has led the World Health Organization (WHO) to classify it as one of world leading ‘neglected zoonotic diseases’ [4].

The disease has been known by various names, including Mediterranean fever, Malta fever, Cyprus fever, and undulant fever [1]. Humans are accidental hosts, but brucellosis continues to be a major public health concern worldwide and is the most commonly prevalent zoonotic infection [5,6]. It is caused by the bacteria of the genus *Brucella*, which are cocco-bacilli, 0.5-0.7 µm by 0.6-1.5

µm in size, aerobic, non-sporulating and non-encapsulated, gram-negative bacteria and is classified as α-proteobacteria [7]. Ten species are recognized within the genus *Brucella*. There are six classical species, *B. abortus* (cattle), *B. melitensis* (sheep and goats), *B. suis* (pigs), *B. ovis* (sheep), *B. canis* (dogs) and *B. neotomae* (rodents). Additionally, another four species, such as *B. microti* (rodents), *B. pinnipedalis* (pinnipeds), *B. ceti* (cetacea) and *B. inopinata* (humans), have been recognized more recently [8].

In humans, it is predominantly caused by four different species of *Brucella*, namely, *B. melitensis, B. suis, B. abortus*, and *B. canis [9]*. Although all of these species can cause human brucellosis, *B. melitensis* is the most prevalent worldwide and is known as the main causative agent of human brucellosis [9,10]. The infection of *Brucella* species is commonly mediated by direct contact with the placenta, abourted fetus, and vaginal discharges or byproducts from the infected animals [11]. The typical route of infection is either direct ingestion or via mucous membranes, broken skin, and in rare cases intact skin [1,12]. In addition, in utero transmission, person-to-person transmission, and transmission associated with tissue transplantation have been observed in a few cases [13]. Aerial bacteria also remain a severe threat of infection, either by inhaling the organisms or through the conjunctiva. Brucellosis also spreads via vertical transmission by infecting newborn calves and lambs in the uterus [14].

Clinically, brucellosis is characterized by one or more of the following signs: abortion is typically one of the clinical signs of the pregnant females with excretion of the organisms in uterine discharges and in milk, while orchitis and epididymitis are typical clinical signs of the male. Infertility, rarely arthritis, headaches, weakness and undulating fever are commonly known signs in humans [9]. Laboratory tests, such as screening and confirmatory tests are very important tools for the correct identification of the disease in both humans as well as animals [15]. Even if many serologic tests are available for the detection of antibodies against antigens, the isolation and identification of the causative bacteria is the gold standard for the diagnosis of brucellosis [16]. This enables strategic measures for controlling and preventing the disease in both animals and humans [17]. Since the disease has no effective treatment, prevention and control methods should be undertaken to mitigate its impacts [18]. This communication reviews the biology, pathogenicity, virulence factors, epidemiology, risk factors, clinical signs, laboratory diagnosis, public health significance, economic importance, prevention and control measures with respect to both animal and human brucellosis.

2. Review

2.1. Biology of *Brucella*

The genus *Brucella* resides within the family Brucellaceae, order Rhizobiales, class Alphaproteobacteria and phylum Proteobacteria [16]. It is coccobacilli or short rods, usually arranged singly but sometimes in pairs or small groups. The organisms are gram-negative, facultative intracellular parasites, and during an infection, they survive and multiply in macrophages. The bacteria adapt to the acidic pH, low levels of oxygen, and low levels of nutrients within the macrophages [19]. *Brucella* is a genus that creates two forms of lipopolysaccharide (LPS). The smooth forms present complete LPS in the outer membrane, and the rough phenotype does not contain the polysaccharide O-chain [20,21].

These infectious agents are able to produce cytochrome oxidase and catalase, and most of them are able to hydrolyze urea. Bacterial cells are able to survive for a prolonged time in water, aborted fetuses, soil, dairy products, meat, dung, and dust [22]. Carbon dioxide is important for the growth of *Brucella* organisms, especially *B. abortus*, and such organisms, which require carbon dioxide for their growth, are called capnophilic organisms [23]. The ability of the genus *Brucella* to replicate and persist in host cells is directly associated with its capacity to cause persistent disease and to circumvent innate and adaptive immunity [16].

The growth of colonies was first observed on *Brucella* selective agar as early as 72 hours (hrs), and the majority of the isolates were obtained after 96 hrs of incubation at 37°C without CO_2, whereas no growth was observed under CO_2 supply. When examined under a stereomicroscope, the colonies showed a characteristic honey-like appearance with very small, glistening, smooth, round, and pin-point morphology. The cellular characteristics of the isolates showed gram-negative, small coccobacilli arranged singly and in pairs [24].

2.2. Pathogenesis

The ability of *Brucella* species to effectively avoid extracellular killing, invade host cells and successfully colonize and multiply is related to evolutionary mechanisms developed by the organism designed to avoid the host immune response and to enhance survival within its target host [25]. *Brucella* species invade epithelial cells of the host, following entry through mucosal surfaces or macrophages in the intestine. Once *Brucella* species have invaded, usually through the digestive or respiratory tract, they are capable of surviving intracellularly within phagocytic or nonphagocytic host cells [26].

The main targets for this bacterium are macrophages, dendritic cells and trophoblast cells. However, *Brucella* can also multiply within other cells, such as epithelioid cells (HeLa) or murine fibroblasts (NIH3T3) [27]. In macrophages, the pathogen avoids the host immune response; therefore, it can multiply and spread to other tissues using cellular tropism. The *Brucella* strains penetrate the host cells through a zipper-like mechanism [28,29]. The initiation of *Brucella* infection depends on the exposure dose, virulence of the *Brucella species* and natural resistance of the animal to the organisms [17]. Bacteria can spread in a host through the lymph nodes and then translocate to the preferred tissues in the reproductive tract [30]. Therefore, *Brucella* induces acute or chronic infection of the reproductive tract that leads to abortion or severe reproductive tract diseases [31].

2.3. Virulence Factors

Brucella species lack classical bacterial virulence factors such as exotoxins, cytolysins, a capsule, fimbriae, flagella, plasmids, lysogenic phages, endotoxic lipopolysaccharide, or inducers of host cell apoptosis [26]. LPS is an essential virulence factor of *Brucella*, as it prevents complement-mediated bacterial killing and provides resistance against antimicrobial peptides such as lactoferrin [20]. LPS consists of lipid A, oligosaccharide core and O-antigen in gram-negative bacteria [27]. Three features distinguish it from other gram-negative bacteria and characterize lipid A found in *B. abortus, namely,* i) the fundamental component is diaminoglucose instead of glucosamine, ii) longer acyl groups, and iii) lipid A is connected to the core by amide bonds instead of ester and amide bonds [20].

Brucella LPS is a relatively poor inducer of gamma interferon and tumor necrosis factor α, both of which are essential for the elimination of the organism [32]. Another important virulence mechanism of *Brucella* is the BvrR/BvrS two-component regulatory system, which is required for modulation of the host cell cytoskeleton upon *Brucella* invasion, and for regulation of the expression of outer membrane proteins, some of which are required for full virulence [26]. Urease may protect *Brucella* during passage through the digestive tract (stomach) when the bacteria access their host through the oral route. The possibility of production of nitric oxide reductase enzymes helps to protect *Brucella* against low-oxygen conditions inside macrophages [27]. Cyclic β-1,2-glucans, which are also part of the outer membrane, are also required for intracellular survival of *Brucella* [33].

2.4. Epidemiology of Brucellosis

The disease occurs worldwide, except in countries where bovine brucellosis (*B. abortus*) has been eradicated [34]. Brucellosis remains endemic in European Mediterranean, Northern and Eastern Africa, near East countries, India, Central Asia, Mexico and Central and South America countries [3,17]. Although brucellosis is endemic in most areas of the world, in much of Northern Europe, Australia, the US and Canada, it has been eradicated or virtually eradicated from the livestock following lengthy and expensive control programs [35]. Among the members of the *Brucella* group, *B. abortus*, *B. melitensis* and *B. suis* species are not host-specific and may transmit to other animal species; hence, from epidemiological evidence, the three species, namely *B. abortus*, *B. melitensis*, and *B. suis* have distinct host preferences but all have a wide range of host species, including humans [36].

2.4.1. Risk Factors in Animals

2.4.1.1. Management Factor

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 an infected herd into a non-infected susceptible herd [26]. Hence, lack of strict movement control of animals from one area to another, lack of proper hygienic practices and good husbandry management play a great role in the increase in the prevalence of brucellosis [17]. In a previous report from Uganda that estimated the prevalence and risk factors for brucellosis among goats, it was observed that hiring caretakers instead of owners looking after the animals was a major risk factor for brucellosis [37].

2.4.1.2. Agent Factor

Brucella is an intracellular pathogen that is able to survive and replicate within phagocytic cells. It can persist on fetal tissues and soil or vegetation for 21-81 days depending on month, temperature, and exposure to sunlight [38]. *Brucella* bacteria can also survive in cold areas and froozen meat for long periods of time [39]. It has been recovered from the fetuses and from manure that has remained in a cool environment for > 2 months. *Brucella abortus* field strain persisted up to 43 days in soil and vegetation at naturally contaminated bison birth or abortion sites. The organisms are able to survive within host leukocytes and may utilize both neutrophils and macrophages for protection from humoral and cellular bactericidal mechanisms during the period of haematogenous spread [17]. The congregation of a large number of mixed ruminants at water points facilitates spread of the disease [9].

2.4.1.3. Host Factors In Animals.

Population density (number of animals to land area) is attributed to increased contact between susceptible and infected animals. The health status of the animals may also play an immense role in the acquisition and spread of the disease infection [17]. Therefore, host factors associated with the spread of brucellosis within a herd include unvaccinated animals in infected herds, herd size, population density, age, sexual maturity, use of maternity pens, and close living with wild animals [38].

2.4.1.4. Environmental and Climatic Factors

The survival of the organism in the environment plays an important role in the epidemiology of the disease [40]. *Brucella* may retain infectivity for several months in water, aborted fetuses and fetal membranes, feces and liquid manure, wool, hay, on buildings, equipment, and clothes. The organism is also able to withstand drying, particularly in the presence of extraneous organic material, and will remain viable in dust and soil [17].

2.4.2. Risk Factors of Human Brucellosis

2.4.2.1. Occupational Exposure

Brucellosis is an occupational hazard with those particularly at risk either living in close proximity with animals or handling them; laboratory workers, abattoir workers, farmers, and veterinarians are at high risk of acquiring the infection [3,39,41]. Handling aborted materials or attending retained placenta or dystocia without protective gear is a common practice for most field veterinary assistants, abattoir workers, and in many rural pastoral settings [16,41,42].

2.4.2.2. Oral Route

Dairy products and raw camel milk are the main sources of infection for people who do not have direct contact with animals [43,44]. In contrast to dairy products, the survival time of *Brucella* in meat seems extremely short, except in frozen carcasses where the organism can survive for years [39].

2.4.2.3. Age and Sex

The disease is very largely occupational, and the majority of cases are males between the ages of 20 and 45 years [44]. In situations where enforcement of hygienic measures is very difficult, the whole population is at risk, and many cases occur in women and children. In nomadic societies, adults have often been exposed to infection at an early age, and do not manifest acute disease [38].

2.4.2.4. Pregnancy and Breastfeeding

Brucellosis is one of the diseases that poses health hazards during the course of pregnancy and carries the risk of spontaneous abortion or intrauterine transmission to the infant. In any event, prompt diagnosis and treatment of brucellosis during pregnancy can be lifesaving for the fetus. Occassionlly, human-to-human transmission from lactating mothers to their breastfed infants has been reported [6].

2.4.2.5. Seasons

In humans, the prevalence of the disease is high in the summer season. Considering the standard incubation period of 2-4 weeks and the fact that lamb slaughter is traditionally at a peak during the Easter period, it might be expected that occupational exposure would result in a peak of human cases between March and May. The observed peak between April and June could be related to the production and consumption of fresh cheese, starting just after lamb slaughter [45].

2.4.3. Source of Infection and Mode of Transmission

Both vertical and horizontal transmissions of brucellosis exist in animals. Horizontal transmission occurs through ingestion of contaminated feed, skin penetration via conjunctiva, inhalation, and udder contamination during milking or by licking the discharge of an animal, newborn calf or retained fetal membrane [39]. A fetus can be infected in the uterus or suckling of infected dams. Congenital infection that occurs during parturition is frequently cleared, and only a few animals remain infected as adults [46]. Venereal infections can also occur and are mainly infected with *B. suis* infections. The importance of venereal transmission varies with the species; it is the primary route of transmission for *B. ovis*, *B. suis,* and *B. canis. Brucella abortus* and *B. melitensis* can be found in semen, but the venereal transmission of these organisms is uncommon [47]. In humans, brucellosis is spread through contact with blood, body tissues, or body fluids of infected animals. The most common method of infection is the consumption of unpasteurized milk and dairy products [17]. In the laboratory and probably in abattoirs, *Brucella* can be transmitted through aerosols, contact with laboratory cultures and tissue samples, and accidental injection of live *Brucella* vaccines [48].

2.5. Clinical Signs

2.5.1. In Animals

Clinically, the disease is characterized by one or more of the following signs in animal species: abortion, retained placenta, orchitis, epididymitis and, rarely, arthritis, with excretion of the organisms in uterine discharges, and in milk [1,9]. Infertility is a common sequel of animal brucellosis and is one of the factors that is responsible for the negative impact on the economy. In horses, *B. abortus* and occasionally *B. suis* can cause inflammation of the supraspinous or supraatlantal bursa; these syndromes are known, respectively, as fistulous withers or poll evil [1,39]. The bursal sac becomes distended with clear, viscous, straw-colored exudates, and develops a thickened wall. Fistulous withers are the most common clinical sign in equine brucellosis, while some horses appear to suffer a generalized infection with clinical signs, including general stiffness, lameness, fluctuating temperature, and lethargy [9,49].

2.5.2. In Humans

Human brucellosis is characterized by a variable incubation period (from several days up to several months) and is an acute or sub-acute febrile illness, and complication affecting any organ and systems [39]. General symptoms of brucellosis are often vague and similar to those of flu [38]. These symptoms include symptoms of continued, intermittent or irregular fever of variable duration, with headaches, weakness, profuse sweating, chills, depression, weight loss, abdominal pain, and cough [1,3,41]. Localized suppurative infections may also occur. Abortion may also occur during the early trimesters of pregnancy [16,50].

2.6. Diagnosis

2.6.1. Bacterial Isolation

Although there are many diagnostic methods for *Brucella* species, isolation and culturing of the organism are the gold standard tests [26]. All *Brucella* strains are relatively slow growing, and because the specimens from which isolations are commonly performed, attempted, are frequently heavily contaminated and therefore, the use of a selective medium, such as Farrell's medium, is advocated [5]. Incubation normally continues for 72 hours, but a negative diagnosis may only be declared after a weeklong incubation. Specimens that may be used for *Brucella* isolation include fetal stomach fluid, spleen, liver, placenta, lochia, milk (especially colostrum or milk within a week of calving), semen and especially supramammary (chronic and latent infections) and retropharyngeal (early infections) lymph nodes, which are preferred, but iliac, prescapular and parotid lymph nodes can also be used. *Brucella* species colonies are elevated, transparent, convex, with intact borders, smooth, and a brilliant surface [17]. The colonies have a honey color under transmitted light. The optimal temperature for culture is 37°C, with a temperature range of 20°C to 40°C, and the optimal pH ranges from 6.6 to 7.4. Some *Brucella* species require CO_2 for growth. Typical colonies appear after 2 to 30 days of incubation, but a culture can only be considered negative when no colonies appear after 2 to 3 weeks of incubation [47].

2.6.2. Modified acid fast Stain

The disease can be confirmed by demonstration of the bacteria in the smears. The smears were made from vaginal discharges, placenta, colostrum, fetal stomach fluid or of the aborting cow's lochia, and the abomasum of the aborted fetus using modified Ziehl-Neelsen (MZN) stain [17]. Impression smears may be taken from freshly cut and blotted tissue surfaces, e.g., placenta cotyledons, by firmly pressing the slide surface against the tissue. Allow to air dry and heat fix smears. In MZN-stained smears, the bacteria appear as red intracellular coccobacilli, whereas most other bacteria stain blue [51].

2.6.3. Serological Tests

Serological tests are crucial for the laboratory diagnosis of brucellosis since most control and eradication programs for brucellosis depend on these methods [52]. They can be broadly divided into two groups: screening tests and confirmatory tests [16]. Although several serological tests have been used for the laboratory testing of brucellosis, no single test is convenient in all epidemiological investigations due to problems of sensitivity and/or specificity [53,54]. The most common serological tests used in brucellosis are the serum agglutination test, Rose Bengal plate test, and indirect enzyme linked immunosorbent assay [3,26]. The Rose Bengal plate test (RBPT) is the most widely used screening test for brucellosis in both humans and animals for its easy application and apparent simplicity of reading [3]. However, interpretations of the RBPT results can be affected by personal experience [55].

The drawbacks of RBT include low sensitivity, particularly in chronic cases, relatively low specificity in endemic areas, and prozones that make strongly positive sera appear negative in RBT [56]. The Milk RingTest (MRT) is also an excellent screening test for dairy cattle [1,16]. MRT is a simple and effective serological method but can only be used with cow's milk [1]. A drop of haematoxylin-stained antigen is mixed with a small volume of milk in a glass or plastic tube [52]. MRT is applicable to the entire herd and yields a rough picture of the status of infection and is very uncertain at the individual animal level. It has some drawbacks, such as less reliability in large herds, and inability to be used for male animals [26].

The complement fixation test (CFT) is a widely used confirmatory test for brucellosis. Due to its high accuracy, complement fixation is used as a confirmatory test for *B. abortus*, *B. melitensis*, and *B. ovis* infections, and it is the reference test recommended by the Organization for Animal Health (OIE) for international transit of animals [57]. In most cases, CFT is used on RBPT-positive sera, but similar to RBPT, it is also affected to a large extent by the misuse of the strain 19 vaccine, particularly when recent or repetitive vaccinations have been used in sexually mature heifers and cows. It is almost impossible to prescribe strict cutoff readings that indicate infection, particularly when S19 vaccination reactions play a role due to their misuse [17]. Some of the problems of CFT are few positive reactions, sometimes negative results in the early stage of infections, and the test is rather expensive and complicated. Other problems include the subjectivity of the interpretation of occasional direct activation of complement by serum (anti complementary activity) and the inability of the test for use with hemolyzed serum samples. False positive results may also occur in animals infected with organisms antigenically related to *Brucella* *[9]*.

Enzyme-linked immunosorbent assay (ELISA) has become popular as a standard assay for the diagnosis of brucellosis [1]. It is an excellent method for screening large populations for *Brucella* antibodies and for differentiation between any acute and chronic phases of the disease [17]. The ELISA method poses a great opportunity to identify all four antibody classes (IgM, IgG1, IgG2 and IgA) [58]. The ELISA is a very good control test in brucellosis-free areas and for survey testing of areas where no vaccination has been performed, but complicated and cannot be carried out everywhere, especially where vaccination has been done and is still not well standardized [26].

The serum agglutination test (SAT) is one of the standard serological tests used for the diagnosis of brucellosis [41,59]. It is easy to perform and does not require expensive equipment and training. SAT measures the total quantity of agglutinating antibodies IgM and IgG. This test is based on the reactivity of antibodies against the smooth lipopolysaccharide of *Brucella*. Excess antibodies resulting in false negative reactions due to the prozone effect can be overcome by applying a serial dilution of 1:2 through 1:64 of the serum samples, thus increasing the test specificity [60]. Drawbacks of the serum agglutination test include the inability to diagnose *B. canis* infections and the appearance of cross-reactions of IgM immunoglobulins with *Francisella tularensis*, *Escherichia coli* O116 and O157, *Salmonella urbana*, and *Yersinia enterocolitica* O:9. Some of these shortcomings can be overcome by modifications, such as the addition of EDTA, 2-mercaptoethanol, or antihuman globulin [52].

2.6.4. Molecular Tests

Polymerase chain reaction (PCR) is an *in vitro* technique for nucleic acid amplification, which is commonly used to diagnose infectious diseases. PCR is now one of the most frequently used assays for the diagnosis of human brucellosis [3,61]. PCR and/or its variants, based on the amplification of specific genomic sequences of the genus, species or even biotypes of *Brucella* species, are the most broadly used molecular techniques for brucellosis diagnosis [62]. Real-time PCR is more rapid and more sensitive than conventional PCR. It does not require post-amplification handling of PCR products, thereby reducing the risk of laboratory contamination and false positive results. Real-time PCR assays have been recently described to test *Brucella* cells [17].

2.7. Public Health Importance

Brucellosis has been reported in 100 different countries worldwide and is a serious threat not only to livestock but also to human health globally [3]. Despite its impact on economic status in affected countries, it is also associated with high morbidity, both for humans and animals in developing countries [63]. During a severe outbreak of brucellosis in dairy buffaloes, two animal attendants and one veterinarian contracted *Brucella* infection. All three persons developed clinical signs of brucellosis, including fever, chills, anorexia, weakness, headache, joint pain, sweating, and coughing. The diagnosis was confirmed by the demonstration of a high titre of *Brucella* agglutins in the sera by a standard tube agglutination test in the sick induduals, and all patients received treatment with antibacterial antibiotics and other supportive drugs for 6 weeks to 10 weeks [41]. Brucellosis outbreak was observed where four persons from a poor family of Indian village were affected. All four patients were young male adults who consumed infected raw goat milk [3]. Currently, half a million cases of brucellosis occur in humans around the world annually [3]. The prevalence of infection in animal reservoirs is key to its occurrence in humans [26]. It is a significant health risk for the entire community since there is close contact between humans and their livestock through sharing the same housing enclosures. The expansion of animal industries, the lack of hygienic measures in animal husbandry, and poor food handling partly account for brucellosis as a significant public health hazard [39].

All ages of human beings are susceptible, and even congenital cases have been recorded [44]. The prevalence of infection in animal reservoirs is key to its occurrence in humans. The prevalence of human brucellosis differs between areas and has been reported to vary with standards of personal and environmental hygiene [8]. *Brucella* can be used as bioterrorism to attack human and/or animal populations [44].

2.8. Economic Importance of Brucellosis

The epidemiology of brucellosis is complex. The important factors that could contribute to the occurrence and spread of livestock, among others, include farming systems and practices, farm sanitation, livestock movemen, and sharing of grazing lands. Brucellosis occurring worldwide in domestic and game animals as well as humans creates a serious economic problem for intensive and extensive livestock production systems [26].

The disease is a major veterinary and human health importance in the economies of affected countries, and it has many economic impacts [40,64]. The economic losses of brucellosis include losses due to abortion in the affected animal population, diminished milk production, *Brucella* mastitis and contamination of milk, culling and condemnation of infected animals due to breeding failure, endangering animal export, human brucellosis causing reduced work capacity through sickness, government costs on research and eradication schemes, and losses of financial investments [16]. Bovine brucellosis causes an estimated financial loss of US Dollar 344 billion to the livestock industry worldwide. It is estimated that annual losses from bovine brucellosis in Latin America are approximately US$ 600 million [3].

2.9. Prevention Measures of Brucellosis in Animals

The aim of prevention and control programs in animals is to reduce the impact of a disease on human health and its economic consequences. The common approaches used to prevent brucellosis include management and biosecurity, hygienic disposal of aborted fetuses, fetal membrane and discharges with subsequent disinfection of contaminated area, test and isolation/slaughter, and vaccination [1,65].

2.9.1. Management and Biosecurity

The use of appropriate management and biosecurity measures is of critical importance to prevent the entrance of the disease in a naïve epidemiological unit. These strategies include the implementation of quarantine before the introduction of new animals, the control of animal movements, the isolation of pregnant females before parturition, and quality control of semen [66,67].

2.9.2. Test and Isolation/Slaughter

In most cases, testing and slaughter of positive animals is only successful in reducing the incidence if the herd or flock prevalence is very low. Retention of positive animals is less hazardous if the remaining animals have been vaccinated but should only be considered as a last resort. The immediate slaughter of test-positive animals is expensive, and requires animal owner cooperation and compensation [68].

2.9.3. Hygiene

The goal in the application of hygiene methods to the prevention of brucellosis is to reduce the exposure of susceptible animals to those that are infected or to their discharges and tissues. Hygienic measures are essential to limit and control the bacterial load in the environment, decreasing the possibility of contact with viable *Brucella* species, and should be systematically implemented. Removal of abortion products, full cleaning and disinfection of premises and elimination of waste is needed [1,69,70].

2.9.4. Control of Animal Movement

Animals should be individually identified by brand, tattoo or ear tag. Unauthorized sale or movement of animals from an infected area to other areas should be forbidden. This applies to the transport of animals and of certain animal products within countries as well as between countries, following the general principles and procedures as specified in the International Zoo-sanitary Code [44].

2.9.5. Vaccination

There is general agreement that the most successful method for the prevention and control of brucellosis in animals is vaccination [71]. Vaccination is used to increase the population’s resistance to the disease. It is accepted as the most economically feasible measure to control animal brucellosis in endemic regions [72]. Three important vaccines are available to control brucellosis. The RB51 and S19 vaccines are used against *B. abortus* infections in bovids, and Rev1 is used against *B. melitensis* in small ruminants [73]. Vaccine decreases the likelihood of an abortion event, which in turn breaks the cycle of transmission, and protects the remaining animals in the herd [74].

2.9.6. Chemotherapy

It is mostly not successful because of intracellular sequestration of the organisms in the lymph nodes, mammary glands, and reproductive organs. If necessary, the treatments often given are sulphadiazine, streptomycin, chlortetracycline, and chloramphenicol [9].

2.10. Prevention of Brucellosis in Humans

Control and eradication strategies vary between developed and developing countries. However, the burden of brucellosis infection is greatest in developing countries. In developed countries, such as the United States, great strides have been made since the initiation of and provision of funding for control and eradication efforts [75]. The most rational approach for preventing human brucellosis is control and eradication of the infection in animal reservoirs. As the ultimate source of human brucellosis is direct or indirect exposure to infected animals or their products, prevention must be based on elimination of such contact [76].

2.10.1. Hygiene and Sanitation

Good hygiene, correct precautions and protective clothing are very important in preventing occupational exposure [77]. All persons carrying out high-risk procedures should wear adequate protective clothing [1,44,78,79]. Proper disposal (burial or burning) of placentas, nonviable fetuses, and disinfection of contaminated areas should be performed thoroughly [1,16,44]. Additionally, pasteurization should apply to all milk for human consumption, whether to be drunk without further processing or to be used for making other food products, and avoiding the practice of eating raw meat is important in preventing food-borne brucellosis [1,78].

2.10.2. Safety Measures in the Laboratory

Each laboratory should have written procedures addressing the use of equipment (especially equipment that may generate aerosols); disinfection of equipment and contaminated materials, handling and processing samples; spill containment and cleanup; and waste handling [16].

2.10.3. Vaccination

Safe and effective vaccines for the prevention of human brucellosis are not generally available [80]. Human vaccines in endemic areas could prevent disease transmission resulting from consumption of contaminated food products as well as potential bioterrorism or biowarfare agents, and protection against aerosol challenge [81].

2.10.4. Chemotherapy

The optimal treatment for brucellosis is a combination regimen using two antibiotics since monotherapies with single antibiotics have been associated with high relapse rates. The combination of doxycycline with streptomycin is currently the best therapeutic option with fewer side effects and fewer relapses, especially in cases of acute and localized forms of brucellosis, and its regimen is considered the gold standard treatment for intracellular *Brucella* [26,82].

2.10.4. Prevention of Brucellosis through One Health Approach

A very important approach for the prevention of brucellosis is that it is gaining increasing recognition around the world in recent years as the One Health approach. In the One Health Framework, veterinary, medical, environmental, and allied professionals and experts collaborate together with the aim of identifying possible risk factors for this infection and designing a suitable approach to combat the infection [38]. The dissemination of educational information about disease prevention to regions where *Brucella* infection is endemic is, therefore, essential for controlling the disease [83]. The development of an effective veterinary infrastructure is an important step to mitigating the disease in humans [84].

3. Conclusion

Brucellosis is a worldwide bacterial zoonotic disease affecting both humans and many species of animals. It has a high prevalence in many African countries and a very high economic and public health impact. Its impact on public health is very well related to the infected animal species from which transmission to humans occurs. The disease can be transmitted from infected animals to human beings through several routes. It causes considerable losses in animals as a result of abortion and a reduction in milk yield. Brucellosis is a special hazard to occupational groups. It is a highly prevalent disease of animals and humans in many countries of the world including Ethiopia and India. Vaccination and management practices, such as rearing of brucellosis-free animals, isolating and restricting movement of infected and/or suspected animals, incineration or burial for proper disposal of animal discharges and wastes, formulating a schedule for cleansing and disinfection of animal houses, feeding and watering troughs, and understanding proper hygienic practices in all stages can play a significant role in reducing its prevalence. Generally, there is no single prevention strategy that check the transmission of brucellosis amongst animals and humans. It is emphasized that veterinarians, medical health professionals, farmers, slaughter houses workers, and the community should collaborate through One Health approach to prevent and control brucellosis in humans and animals.

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Conflict of Interest

The authors declare that they do not have conflicts of interest.

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