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A Review On Human Brucellosis: An Important Occupational Hazard

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Abstract:
Human brucellosis is a re-emerging and neglected zoonotic disease caused by Brucella spp., with Brucella melitensis being the principal cause worldwide. Despite the disease's prevalence, serological surveillance is not routinely practiced, even in countries where Brucella is endemic. Although eradication efforts have been successful in many developed and developing countries, brucellosis continues to pose a significant health risk to both animals and humans. Transmission to humans occurs by direct or indirect contact with infected animals or their products. Veterinary professionals, especially those conducting per-vaginal examinations without proper protective gear, and animal handlers are particularly vulnerable to infection. The pathogenesis of brucellosis is complex, involving bacterial invasion of host cells, immune evasion, and the potential for chronic infection. In humans, brucellosis often becomes chronic, but in acute cases, it presents as undulant fever with nonspecific symptoms. To reduce morbidity and mortality, early diagnosis and timely antibiotic treatment are most important. For diagnosis of Brucella spp. reliable, rapid, sensitive, specific, easy-to-perform, and automated detection systems are urgently required. Currently, there is no safe and effective vaccine available for humans. Prevention relies on controlling the disease in domestic livestock, primarily through mass vaccination, effective heat treatment of dairy products, and hygienic precautions to minimize occupational exposure. Treatment requires prolonged antibiotic therapy with a combination of drugs. To control human brucellosis, awareness programs, safe livestock practices, and timely diagnosis are essential.

Keywords: *Brucella spp; Clinical signs; Control; Epidemiology; Pathogenesis; Serological surveillance; Treatment.*

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I. Introduction And Background

Human brucellosis, also known as undulant fever, is a re-emerging and neglected zoonotic disease caused by facultative intracellular gram-negative, partially acid-fast coccobacilli of the genus Brucella (family Brucellaceae). These bacteria lack a capsule, flagella, endospores, or native plasmids. Brucella typically infects animals such as cattle, sheep, pigs, and dogs, while human brucellosis is caused by four pathogenic species: *Brucella melitensis, B. suis, B. abortus,* and *B. canis* [1]. The World Health Organization classifies brucellosis as a neglected disease due to the limited attention it receives from global health systems [2]. The disease is known by many names in various regions where it occurs, such as Malta fever, Mediterranean fever, Cyprus fever Gibraltar fever and undulant fever[3]. Because of its advesrse impact on public health, economics, and global trade, Brucellosis is a priority disease for the World Organization for Animal Health (WOAH) [4]. It is often regarded as a disease of poverty, imposing a significant socioeconomic burden. It typically begins as a debilitating acute infection but can progress to a chronic condition with multiple complications [5].

Brucellosis with an estimated 2.4 billion people at risk of infection.is one of the most prevalent zoonotic diseases worldwide. According to various estimates, nearly 0.5 to 2.1 million new cases are reported annually [6,7]. In animals, brucellosis is known as Bang's disease, epizootic abortion, or contagious abortion [8]. While the disease has been eradicated in a few high-income countries, it remains widespread in low-income regions, leading to significant health, economic, and livelihood burdens [9]. Although eradication efforts have succeeded in many developed nations, brucellosis is still endemic in parts of Africa, the Mediterranean, Asia, and the Americas [10]. Despite efforts to eradicate it, brucellosis continues to pose a significant health threat in both animals and humans in numerous countries [11]. In regions such as Israel, Kuwait, Brazil, Saudi Arabia, and Colombia, brucellosis is considered a re-emerging problem, particularly due to the increasing incidence of *B.* melitensis or *B. suis biovar 1* infection in cattle [12].

Diagnosing brucellosis requires clinical evaluation, laboratory tests including serological tests, blood cultures, , and molecular approaches. However, the non-specific nature of symptoms and challenges in obtaining appropriate samples create diagnostic difficulties [13]. Treatment typically involves a combination of multiple

antibiotics, though the rise of antibiotic-resistant Brucella strains presents significant challenges [14]. Vaccination of potential carrier animals, particularly within livestock populations, has shown promise in controlling the spread of brucellosis [15].

The lack of pathognomonic symptoms and the wide range of clinical manifestations make human brucellosis difficult to diagnose, often resembling other febrile illnesses. Therefore, laboratory tests are crucial for diagnosis. Managing brucellosis requires sustained research and interdisciplinary collaboration between public health officials, healthcare providers, and veterinary experts to develop effective strategies for controlling and preventing the disease. This includes understanding exposure risks, diagnostic limitations, treatment practices, and preventive surveillance programs [16].

Despite ongoing efforts to curb the spread of brucellosis, it continues to challenge public health systems worldwide, resulting in livestock productivity losses and significant economic impacts [17]. This review focuses on the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment of brucellosis. It also discusses the latest research on Brucella species, their transmission modes, and the global health implications of this zoonotic disease.

II. Review

Features of Brucella Species: Brucellae are gram-negative, facultative intracellular organisms that can take the form of rods, cocci, or coccobacilli. They thrive in cool, wet environments but are susceptible to most common disinfectants. While they can survive thawing and freezing, they are easily killed by pasteurization [18,19]. These bacteria are catalase, urease and oxidase positive. The Brucella species with the highest pathogenicity in humans (*B. abortus, B. melitensis, and B. suis*) possess an O-polysaccharide (O-PS) side chain on their lipopolysaccharide (LPS) component, giving them a smooth colony phenotype. In contrast, rough colony phenotypes like *B. canis* and *Brucella ovis* lack the O-PS antigen, a characteristic that helps differentiate them from smooth species in serologic assays [20].

Epidemiology:

Veterinary professionals are at high risk for brucellosis due to constant exposure to infected animals. Studies have reported high seroprevalence of Brucella antibodies among veterinarians and para-veterinarians [21,22]. While approximately 500,000 human cases of brucellosis are reported worldwide each year, but exact number is higher likely due to underreporting, ranging from 5,000,000 to 12,500,000 annual cases [23]. Despite these high numbers, brucellosis continues to pose a significant disease burden in low- and middle-income countries (LMICs), where it receives insufficient attention from health systems. Brucellosis is listed among the top neglected zoonoses by the World Health Organization (WHO) [24]. Brucellosis remains one of the most widespread bacterial diseases worldwide, with particularly high prevalence in regions like the Mediterranean, Middle East, Asia, Africa, South and Central America, and the Caribbean [25,26]. Countries with the highest reported incidence include Iran, Kyrgyzstan, Tajikistan, Kazakhstan, Azerbaijan, Turkmenistan, Armenia, and Uzbekistan [27,28]. Recent studies have revealed that the global incidence is higher than previously estimated, with 1.6 to 2.1 million new cases annually [29]. In Latin America, areas like California in the United States, Mexico, and Peru have reported numerous cases among older Latino men, often attributed to the consumption of unpasteurized Mexican-style soft cheese [30]. In the European Union, the European Food Safety Authority (EFSA) recorded a decline in brucellosis cases from 735 in 2008 to 352 in 2011, indicating the success of intervention measures [30]. *Brucella canis* cause of canine brucellosis in Europe is a zoonotic threat to public health. The lack of awareness and comprehensive surveillance among dog owners and veterinarians has complicated efforts to manage this disease. Men aged 45-64 were affected at more than double the rate of women in the same age group [31]. In sub-Saharan Africa, the prevalence of brucellosis in livestock ranges from 0.2% to 43.8% in cattle, 0.0% to 20.0% in goats, and 0.0% to 13.8% in sheep. Among humans in the region, the prevalence ranges from 0% to 55.8%, underscoring the significant impact of brucellosis [32].

In rural India, brucellosis is endemic, with a seroprevalence of 15.1% (95% CI: 15.9-19.8%) due to the common practice of agriculture and livestock farming, which facilitates transmission through close human-animal interactions[33]. Studies measuring the prevalence of human brucellosis, particularly among veterinary professionals in Indian states like Karnataka, Punjab, Maharashtra, and Assam, have reported seroprevalence rates ranging from 2.4% to 55.0% [21,34,35,36,37,38]. A 2013 study in Odisha, focusing on high-risk groups, found a maximum seroprevalence of 9.09% 39. In Punjab, herd-level and individual seroprevalence estimates in cattle and buffalo have been as high as 65.5% and 21.4%, respectively [40,41]. Another study in Punjab reported an overall brucellosis prevalence of 12.09%[42]. Close interactions with stray and wild animals, consumption of dairy products, unpasteurized milk, and improper waste disposal are key factors contributing to human brucellosis. In rural Pakistan, around 16% of the population in close contact with animals tested seropositive for brucellosis [43]. High-risk professionals (6.9%) and pregnant women (8.5%) have been identified as particularly vulnerable [44,45]. Adults and females are at higher risk, with males aged 25-40 years most frequently affected. Interestingly, higher

infection rates were observed in female children (14.3%) compared to male children (10.9%) [46,47]. In India, it is estimated that less than 10% of human brucellosis cases are recognized and treated. A study in West Bengal found a seropositivity rate of 15.8% among tested patients, with the highest percentage (23.5%) falling within the 51-60-year age group. Male animal handlers exhibited higher seropositivity than their female counterparts [48,49]. The recent rise in brucellosis cases in India has been linked to the growth of the dairy industry, which has led to increased livestock populations. A high seroprevalence of anti-Brucella antibodies has been noted among veterinarians, veterinary pharmacists, and animal handlers due to their involvement in livestock health and management[49]. Brucella infection is more prevalent in individuals with weakened immune systems, such as those under stress or suffering from diseases like HIV[50]. In brucellosis endemic areas seasonal trends show marked increase during spring, with highest prevalence from March to June[51].

Mode of transmission:

Brucellosis is transmitted to humans through various routes, primarily through direct or indirect contact with infected animals or their products. One of the most common ways humans become infected is by consuming raw or unpasteurized dairy products, such as milk, sour milk, camel milk, and cheese, as well as by consuming contaminated animal products like meat or carcasses[52, 53]. Camel milk, in particular, is a significant source of infection in regions like the Middle East and Mongolia. Inhalation of aerosols in slaughterhouses and meat processing facilities is a major concern which can also lead to airborne transmission of the Brucella organism[7]. Additionally, secretions from infected animals serve as a common vehicle for human transmission [54]. Laboratory-acquired brucellosis is a major health hazard for workers handling virulent or attenuated Brucella strains. Infection can occur through accidental inhalation, ingestion, or mucosal contact, making it one of the more common laboratory-transmitted diseases. This has been reported in clinical, research, and production laboratories [48, 55, 56.] Other means of transmission include skin abrasions or inhalation of airborne particles, such as those from animal manure, which further increases the risk for those regularly handling livestock [57]. Brucellosis is also a significant occupational hazard for individuals working in livestock-related fields, such as veterinarians, animal handlers, slaughterhouse workers, farmers, and laboratory personnel [42, 58].

In India, where approximately 80% of the population involved in agriculture lives in close contact with domestic or wild animals leading to the high risk of contracting brucellosis [48, 59]. While human-to-human transmission is exceedingly rare, it can occur under certain circumstances, such as from an infected mother to her unborn child during pregnancy [60, 61]. In veterinarians, occupational exposure often results from failing to use proper personal protective equipment (PPE) while performing tasks like diagnosing pregnancies, assisting with dystocia, or handling retained placentas[62]. Animal handlers engaged in tasks such as vaccination or deworming are exposed to various transmission routes, including contact with secretions from diseased animals and accidental needle-stick injuries during vaccination. Additionally, handling contaminated biological materials or live attenuated anti-brucellosis vaccines poses a risk for human infection[61]. Though the bacterial load in animal muscle tissue is generally low, consuming undercooked traditional dishes like liver has been linked to brucellosis cases in humans [63].

In developed countries, the disease is more prevalent among wild animals, with the potential for spill over infections posing a threat to humans [64, 65]. In some regions, contact with infected materials like placentas, aborted foetuses, urine, and carcasses accounts for 60-70% of human brucellosis cases [66]. Despite the recognized risk factors, more detailed knowledge about specific occupational risks and their measurements remains limited [49]. However, it is clear that individuals who frequently come into contact with infected livestock are at high risk for Brucella infection [67].

Pathogenesis*:*

Brucella spp. are highly adapted pathogens affecting both humans and animals. These facultative intracellular bacteria do not survive long outside of their host but thrive within the cells of the reticuloendothelial system. They can enter the human body through ingestion, inhalation, or through breaches in the skin or mucosal surfaces [12, 68]. The acidic environment of the stomach provides some protection against oral infection, while human serum opsonizes the bacteria for phagocytosis and exhibits moderate anti-Brucella activity. However, human neutrophils are effective against some strains but are ineffective against *Brucella melitensis*[69]. The pathogenesis of brucellosis involves several unique factors, including lipopolysaccharide (LPS), flagellum, type IV secretion system (T4SS), and the BvrR/BvrS system. These factors facilitate the bacteria's interactions with host cells, the formation of Brucella-containing vacuoles (BCVs), and interactions with the endoplasmic reticulum (ER) during bacterial replication[70, 71, 72]. Brucella spp. penetrate host cells, escape immune responses, and cause chronic infections. They translocate across mucous membranes, spread to regional lymph nodes, and proliferate within macrophages [73, 74]. These bacteria evade macrophage defense mechanisms, leading to prolonged infection[75]. Both opsonized and non-opsonized Brucella can infect macrophages, indicating that adherence and invasion occur directly, and are also mediated by antibodies or complement[75]. Within macrophages, Brucella cells

inhibit phagosome-lysosome fusion, survive, and multiply, eventually disseminating to other cells. Smooth LPS aids in cell entry and immune evasion, altering the infected cell's ability to present antigens to the MHC class II system and thus evading immune system destruction[76]. An outer membrane structural protein, Omp25, and recently identified ribosomal proteins also contribute to Brucella's virulence. The urease enzyme plays a key role in protecting the bacteria during gastric passage, which is crucial for oral infection[77]. The survival of Brucella in the intracellular environment involves a complex interplay of immune evasion mechanisms, including cytokine regulation, such as interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukins IL-2, IL-10, and IL-12, which control bacterial replication within macrophages[75].

Brucella spp. infection leads to granuloma formation characterized by epithelioid cells, polymorphonuclear leukocytes, lymphocytes, and giant cells, with variations depending on the species: B. abortus often shows prominent granulomas, while *B. melitensis* infections present with smaller granulomas and toxaemia, and B. suis infections may result in chronic abscesses in joints and the spleen [69, 78, 79]. Clinical manifestations include fatigue, fever, generalized discomfort, and more severe outcomes like arthritis, osteomyelitis, endocarditis, and meningoencephalitis [70, 71]. The bacteria's ability to manipulate host cell processes, inhibit phagocytosis, disrupt phagocyte function, and prevent apoptosis is key to its pathogenicity. Brucella spp. can evade the immune system and reduce exposure to antimicrobials, complicating treatment [20]. The serological response involves an initial rise in IgM antibodies, followed by predominance of IgG antibodies, with levels decreasing after treatment, although low titers of IgM may persist for months or years [69, 78, 79].

Clinical Signs:

Brucellosis in humans manifest with a wide variety of symptoms affecting various organs. The incubation period ranges from five days to six months, with symptoms potentially persisting for months or years in chronic cases [1]. This variability highlights the importance of a detailed medical and dietary history for accurate diagnosis, particularly in non-endemic regions where infection may result from consuming imported contaminated food.

Common clinical signs include intermittent prolonged fever, migratory joint pain, night sweats, headache, weakness, arthralgia, malaise, depression, diarrhea, abdominal pain, weight loss, and miscarriage. Additional symptoms may include splenomegaly, hepatomegaly, and lymphadenopathy. In severe cases, brucellosis can lead to arthritis, osteomyelitis, spondylitis, epididymitis, and orchitis [13]. The disease may progress to a chronically incapacitating stage with severe complications such as osteoarticular disease, neurobrucellosis, cardiac involvement (e.g., endocarditis), and genitourinary issues (e.g., orchitis, epididymitis, prostatitis) [80]. Brucella spp. exploit host immune defenses to establish chronic infections, leading to a spectrum of clinical manifestations. In acute cases, the disease may present as undulant fever with nonspecific symptoms such as myalgia, arthralgia, and occasional abortions. Chronic cases can manifest with cardiovascular and central nervous system malaise [81]. Patients with chronic brucellosis may experience general malaise and psychiatric symptoms like depression and anxiety. Neurological signs, including Guillain-Barre syndrome and respiratory symptoms can also occur [82]. Death is rare but has been reported, with some cases noting a unique unpleasant odor in the patient's sweat [83]. Complications such as epididymoorchitis and endocarditis are uncommon, with endocarditis being a primary cause of death related to brucellosis [84]. Skin and ocular manifestations such as keratoconjunctivitis, iridocyclitis, uveitis, optic neuritis, cataracts, maculopapular eruptions, panniculitis and abscesses have also been observed [85]. In children, brucellosis can present as haemorrhagic anemia, with severe thrombocytopenia and microangiopathic hemolytic anemia [86].

In animals, brucellosis is manifested by fever, birth of weak calves, abortion storms particularly in the last trimester along with retention of fetal membranes and endometritis. Carrier and vaccinated animals rarely abort and may remain undiagnosed.

Diagnostic Tests:

A thorough history of travel, exposure to animals, and consumption of exotic foods is crucial for diagnosing brucellosis. Prompt and accurate diagnosis is essential due to the specific and prolonged antibiotic treatment required. Diagnostic techniques commonly used for brucellosis diagnosis include serological assays, blood cultures and molecular techniques. Each method has its advantages and limitations concerning sensitivity, specificity, and time required for results, with challenges including sample collection difficulties and non-specific symptoms.

Peripheral blood cultures are used to confirm human brucellosis, especially during bacteremia. Early-stage brucellosis often presents with low-level, persistent bacteremia that can be detected in multiple blood samples. Brucella may periodically re-enter the bloodstream, increasing the risk of spreading to other areas and clinical recurrence. Despite its low virulence in humans, Brucella spp. can be recovered from mildly symptomatic or even afebrile patients [87]. Various blood culture techniques have been employed, including manual monophasic and biphasic approaches, lysis-based blood cultures, blood clot mediums, and automated systems. Automated

blood culture methods, such as the Bactec system, are more effective for recovering Brucella and reducing detection time compared to traditional methods [88]. Automated systems like Bact/ Alert, BActec 9000 series, Vital, and eSP are now preferred for brucellosis detection, offering faster identification of organisms in blood and other bodily fluids. Matrix-Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) mass spectrometry has advanced the classification and identification of Brucella species but remains expensive, limiting its availability, particularly in endemic regions[89].

Serological diagnostics do not directly identify living bacteria or their DNA sequences but detect specific antibodies (IgM and IgG) in patients' sera, indicating previous or ongoing infection. Common serological tests include the Buffered Acidified Plate Antigen Test (BAPAT), Rose Bengal Test (RBT), Serum Agglutination Test (SAT), Standard Tube Agglutination Test (STAT), Complement Fixation Test (CFT), Brucella Coombs Gel Test, Enzyme-Linked Immunosorbent Assay (ELISA), and Polymerase Chain Reaction (PCR)[60,90,91,92]. ELISA and agglutination tests are relatively quick, sensitive, and inexpensive, with ELISA being particularly useful for complex and chronic cases like neurobrucellosis and B. canis infections. One study suggested that ELISA could be an acceptable alternative to blood culture for diagnosing brucellosis, with sensitivity and specificity rates of 100% and 99.2%, respectively[94]. Other advanced methods include Time-Resolved Fluorescent Resonance Energy Transfer (TR-FRET), Fluorescent Polarization Immunoassay (FPA), and Quantum Dot (QD) immunochromatographic tests, which offer various benefits including simplicity, robustness, and point-of-care testing[87]. Modified Ziehl-Neelsen (ZN) staining and Gram stain morphology, combined with the urease test, have been recommended for rapid genus-level identification where further identification facilities are unavailable. While each test has its applications, the gold standard for diagnosis remains the isolation of Brucellae. However, due to the intracellular nature of Brucellae, biohazard risks, and time-consuming procedures, this method is not always preferred. It requires advanced biosecurity measures and highly skilled personnel, and sample submission for isolation may not always be feasible.

Molecular approaches, including nucleic acid amplification tests (NAATs) such as PCR, offer accurate and rapid detection of Brucella DNA at the species level or between vaccine and field strains[95]. These methods both in humans and animals are effective for detecting brucellosis, even in asymptomatic cases. However, because they can detect genetic material from inactive or treated bacteria, a positive result does not always indicate an active infection. Nonetheless, molecular methods offer several advantages over bacteriological isolation, including improved safety, sensitivity, and speed. They enable rapid detection and differentiation of bacterial species, especially those with slow growth rates, and can evaluate genetic material from formalin-fixed, paraffin-embedded tissues [96].

Treatment:

Treatment of brucellosis typically requires a combination of antibiotics administered over an extended period, resulting in a higher burden of disability-adjusted life years lost (DALY) compared to other zoonoses with global distribution[97]. However, due to limited diagnostic facilities, incomplete epidemiological surveillance, and restricted access to treatment in low- and middle-income countries, the DALY for brucellosis may be underestimated. Relapses occur in 5-10% of cases, with some reports suggesting this could be as high as 30% [98, 99]. These relapses generally happen within six months of initial treatment but can occur later in some cases [100]. They are often due to improper choice of antibiotics, inadequate duration of therapy, poor compliance, or a combination of these factors, rather than antibiotic resistance. The World Health Organization recommends treating acute brucellosis in adults with rifampicin (600 to 900 mg) and doxycycline (100 mg twice daily) for a minimum of six weeks [101]. This regimen forms the basis of treatment for all types of human brucellosis. A study revealed that 52 isolates of *B. melitensis* were susceptible to various antibiotics, including tetracycline, doxycycline, streptomycin, rifampicin, ciprofloxacin, ceftriaxone, and ofloxacin, though 15 isolates were inhibited at high concentrations of trimethoprim-sulfamethoxazole [102]. Standard dual therapy with doxycycline and rifampicin has a higher risk of treatment failure compared to triple therapy, which includes streptomycin or levofloxacin. Triple therapy with doxycycline, streptomycin, and hydroxychloroquine for 42 days has a lower failure risk than the doxycycline and streptomycin regimen alone [103]. For acute, uncomplicated brucellosis, full recovery is expected with appropriate antibiotic therapy. In adults and children over eight, doxycycline is typically administered orally for six weeks. To minimize the risk of relapse during the initial 2-3 weeks of therapy, aminoglycosides are often added [26, 71, 104]. Dogs with *B. suis* infection are treated using a combination of doxycycline and rifampicin. In severe cases involving *B. canis* infected dogs, euthanasia is considered, and dual therapy is recommended despite high relapse rates, particularly in males. During complicated cases such as spondylitis, neurobrucellosis, or endocarditis, a prolonged triple therapy regimen including doxycycline streptomycin, gentamicin, and rifampicin is more effective [87]. Rifampicin, with or without cotrimoxazole, has proven safe for treating brucellosis during pregnancy [105]. The emergence of multidrug-resistant Brucella strains in endemic areas is linked to improper antimicrobial use, with antibiotic use in livestock contributing to this issue, posing a public health risk and limiting treatment options [106].

Control of Brucellosis:

Controlling brucellosis in endemic areas is crucial. The most effective way to control human brucellosis is by managing the disease in animals. Brucellosis has been eradicated or controlled in a few developed countries using costly and extensive programs such as animal vaccination and culling infected animals. A "One Health" approach is needed, which integrates human and animal health efforts with livestock holders. To enhance control measures, programs must educate populations at risk. Preventing and controlling brucellosis involves improving hygiene, food safety, surveillance, and increasing awareness among the public and healthcare providers. There is no FDA approved human vaccine for Brucella, although China with limited international approval uses live-attenuated vaccines targeting *B. melitensis* and *B. suis* strains [16, 87, 107]. The development of vaccines remains a promising approach for controlling brucellosis, especially in livestock, though no vaccines are officially approved for humans. The absence of human vaccines hampers disease management efforts [108]. Therefore, controlling animal brucellosis is the most effective strategy to prevent human infection [109]. Various vaccines have been developed for animals, including inactivated, live-attenuated, rough-attenuated, DNA, subunit, nanoparticle-based, vector, and recombinant peptide vaccines [87]. Live-attenuated vaccines like *B. melitensis* Rev. 1 and *B. abortus* S19 have been used successfully in small ruminant and bovine brucellosis control programs worldwide. Despite their success, these vaccines have drawbacks, including potential antibiotic resistance, diagnostic interference, and residual virulence [110]. All available vaccines have limitations, such as causing abortion in target and non-target animals and potentially transmitting brucellosis to humans [5]. However, improvements in recombinant peptide vaccines show promise for overcoming these limitations and offering more effective and safer prevention methods [111]. WHO classifies Brucella in risk group 3, for individuals handling brucella such as such as veterinarians, laboratory workers, and butchers. There is need for highlighting the significant risk and the need for proper protective equipment and training [16, 13]. Accurate and timely data on symptomatic and asymptomatic animal carriers are essential for assessing disease burden. Comprehensive preventive measures throughout the dairy and meat supply chain are necessary, as the disease primarily spreads through consuming raw or undercooked meat and unpasteurized dairy products. All such products should be thoroughly cooked before consumption. Prevention of human brucellosis relies on controlling the disease in domestic livestock, primarily through mass vaccination [112]. Given the high cost of treating animal brucellosis, mass vaccination of livestock should be encouraged, and animal owners should be educated on the importance of vaccination. Despite the clinical efficacy, cost-effectiveness, limited availability of vaccination and lack of awareness contribute to the persistence of brucellosis in many regions of the world. The absence of human vaccines and effective control measures necessitates protective measures by doctors and healthcare workers. Occupational brucellosis can be reduced by wearing protective clothing and barriers when handling stillbirths, products of conception, and cultures [1, 113].

III. Conclusions

This study highlights that individuals in endemic areas who are exposed to infected animals and their products are at a high risk of contracting brucellosis. In brucellosis endemic regions, routine serological surveillance should be implemented. Due to the diverse clinical manifestations and lack of pathognomonic symptoms, laboratory tests are crucial for diagnosing brucellosis. These tests are essential to distinguish the disease from other febrile conditions. Preventing and controlling brucellosis, particularly in high-risk occupational groups, requires a multifaceted approach. This includes improving hygiene, enhancing food safety, and increasing awareness among the public and healthcare providers about zoonotic diseases. Occupation related brucellosis can be mitigated by using protective clothing and barriers while handling stillbirths, products of conception, and cultures. It is important to educate at-risk individuals about precautionary measures to reduce their own risk and to safeguard consumers from brucellosis. Individuals at high risk for brucellosis should be periodically screened to enable early detection and prompt treatment. Veterinary professionals, especially when performing per vaginal investigations in pregnant animals, should be advised to wear double gloves to reduce exposure risk. The prevention of human brucellosis largely depends on controlling the disease in domestic livestock through mass vaccination. A "One Health" approach, which integrates animal and human health efforts, is crucial for effective brucellosis control.

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References

[1] Young Ej: An Overview Of Human Brucellosis. Clinical Infectious Diseases. 1995;21(2):283–289
[2] Who 2023: The Control Of Neglected Zoonotic Diseases. A Route To Poverty Alleviation. Who. 2023., Https:// Www.Who.Int/Publications-Detail-Redirect/9789241594301
[3] Mantur Bg, Amarnath Sk, Shinde Rs. Review Of Clinical And Laboratory Features Of Human Brucellosis. Indian Journal Of Medical Microbiology 2007; 25 (3):188-202

[4] Woah ,2023. Manual Of Diagnostic Tests And Vaccines For Terrestrial Animals 2022. World Organisation For Animal Health. Https://Www.Woah.Org/En/What-We-Do/Standards/ Codes-And-Manuals/Terrestrial-Manual-Online-Access/58 Williams E. Brucellosis And The British Public. Lancet. 1970; 1:1220-1222.

[5] Callaghan. Human Brucellosis. Recent Advances And Future Challenges Infectious Diseases Of Poverty. 2020; 9:101 Https://Doi.Org/10.1186/S40249-020-00715-

[6] Jennings Gj, Hajjeh Ra, Girgis Fy, Fadeel Ma, Maksoud Ma, Wasfy Mo, El-Sayed N, Srikantiah P, Luby Sp, Earhart K, Mahoney Fj. Brucellosis As A Cause Of Acute Febrile Illness In Egypt. Transactions Of The Royal Society Of Tropical Medicine And Hygiene. 2007 ;101(7):707-13. Doi: 10.1016/J.Trstmh.2007.02.027.

[7] Laine C G, Johnson V E, Scott H M & Arenas-Gamboa A M. Global Estimate Of Human Brucellosis Incidence. Emerging Infectious Diseases.2023;(29): 1789–1797. Https://Doi.Org/10.3201/Eid2909.230052.

[8] Wadood F, Ahmad M, Khan, A, Gul St & Rehman N. Seroprevalence Of Brucellosis In Horses In And Around Faisalabad. Pakistan Veterinary Journal. 2009;29: 196-198

[9] Franc Ka, Krecek Rc, Häsler Bn, Arenas-Gamboa Am. Brucellosis Remains A Neglected Disease In The Developing World: A Call For Interdisciplinary Action. Bmc Public Health. 2018;18(1):125. Doi: 10.1186/S12889-017-5016-Y.

[10] Nikokar I, Hosseinpour M, Asmar M. Seroprevalence Of Brucellosis Among High Risk Individuals In Guilan. The Iranian Journal Of Medical Sciences. 2011; 16: 1366–1371.

[11] Jamil T, Akar K, Erdenlig S, Murugaiyan J, Sandalakis V, Boukouvala E, Psaroulaki A, Melzer F, Neubauer H, Wareth G. Spatio-Temporal Distribution Of Brucellosis In European Terrestrial And Marine Wildlife Species And Its Regional Implications. Microorganisms. 2022; 10(10):1970. Https://Doi.Org/10.3390/Microorganisms10101970

[12] Corbel Mj: Brucellosis: An Overview. Emerging Infectious Diseases. 1997; 3:21321.

[13] Franco Mp, Mulder M, Gilman Rh, Smits Hl. Human Brucellosis. Lancet Infectious Diseases. 2007 ;7(12):775-86. Doi: 10.1016/S1473-3099(07)70286-4.

[14] Ariza J, Bosilkovski M, Cascio A, Colmenero Jd, Corbel Mj, Falagas Me, Memish Za, Roushan Mr, Rubinstein E, Sipsas Nv, Solera J, Young Ej, Pappas G. International Society Of Chemotherapy; Institute Of Continuing Medical Education Of Ioannina. Perspectives For The Treatment Of Brucellosis In The 21st Century: The Ioannina Recommendations. Plos Medicine 2007; 4(12): E317. Doi: 10.1371/Journal.Pmed.0040317.

[15] Schurig Gg, Sriranganathan N, Corbel Mj. Brucellosis Vaccines. Past, Present And Future. Veterinary Microbiology. 2002; 90(14):479–496. Doi: 10.1016/S0378-1135(02)00255-9.

[16] Goonaratna C. Brucellosis In Humans And Animals. Ceylon Med J. 2009,52(2):66. Doi: 10.4038/Cmj. V52i2.1028.

[17] Deka R P, Magnusson U, Grace D, & Lindahl J. Bovine Brucellosis.Prevalence, Risk Factors, Economic Cost And Control Options With Particular Reference To India- A Review. Infection Ecology & Epidemiology. 2018; 8:(1). 1555448. Https://Doi.Org/10.1080/20008686.2018.1556548

[18] Santos Rl, Souza Td, Mol Jps, Eckstein C, Paíxão Ta. Canine Brucellosis: An Update. Frontiers In Veterinary Science. 2021; 8:594291. Doi:10.3389/Fvets.

[19] Bramlage Dj, Fortney W, Kesler Rm, Mabray Cj, Mason J W, Reinhold H, Sessions P, Wise A. Best Practices For Brucella Canis Prevention And Control In Dog Breeding Facilities. Usda. 2021, Https://Www. Aphis.Usda.Gov/Animal Welfare/Downloads/Brucella_ Canis_Prevention.Pdf

[20] Pinn-Woodcock, T, Frye E, Guarino C, Franklin-Guild, R, Newman, A P, Bennett J, & Goodrich E L. A One-Health Review On Brucellosis In The United States. Journal Of American Veterinary Medical Association. 2023;261:(4), 451-462. Https: //Doi.Org/10.2460/Javma.23.01.0033

[21] Gemechu M Y & Gill J P S. Seroepidemiological Survey Of Human Brucellosis In And Around Ludhiana, India. Emerging Health Threats Journal 2011; 4: (1) 7361, Doi: 10.3402/Ehtj. V4i0.736

[22] Deepthy B. Department Of Biotechnology And Microbiology. Kannur University; Kannur: 2012. Serodiagnostic Study Of Animal Handlers For Brucellosis. (P. 3.8, Mb) [Google Scholar 1371/Journal.Pmed.0040317.

[23] Hull N C, And Schumaker B A. Comparisons Of Brucellosis Between Human And Veterinary Medicine. Infection Ecology & Epidemiology. 2018; 8:1500846. Doi: 10.1080/20008686.2018.1500846

[24] World Health Organization (Who). Seven Neglected Endemic Zoonoses-Some Basic Facts. Geneva: World Health Organization. 2011.

[25] Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos E V. The New Global Map Of Human Brucellosis. Lancet Infectious Diseases. 2006; 6: 91–99. Doi: 10.1016/S1473-3099(06)70382-6

[26] Bosilkovski M, Edwards Ms, Calderwood Sb. Brucellosis: Epidemiology, Microbiology, Clinical Manifestations, And Diagnosis. Uptodate, United States. 2019.

[27] Pal, M, Gizaw F, Fekadu G, Alemayehu G, & Kandi V: Public Health And Economic Importance Of Bovine Brucellosis: An Overview. Ammerican Journal Of Epidemiology. 2017; 5(2): 27-34.

[28] Khurana Sk, Sehrawat A, Tiwari R, Prasad M, Gulati B, Shabbir Mz, Chhabra R, Karthik K, Patel Sk, Pathak M, Iqbal Yatoo M, Gupta Vk, Dhama K, Sah R, Chaicumpa W. Bovine Brucellosis - A Comprehensive Review. Vet Q. 2021; 41(1):61-88. Doi: 10.1080/01652176.2020.1868616.

[29] Centers For Disease Control And Prevention: Estimates Human Brucella Infections Could Be Four Times Higher Than Previously Thought. Food Safety; 2023. Available From: Https://Www.Food-Safety.Com/Articles/8817-Cdc

[30] Bano Y, Ahmad Lone S. Brucellosis: An Economically Important Infection. Journal Of Medical Microbiology And Diagnosis. 2015;4(4):208. Doi: 10.4172/2161-0703.1000208.

[31] Tao Z, Chen Q, Chen Y, Et Al. Epidemiological Charac Teristics Of Human Brucellosis—China. China Cdc Weekly. 2021;3(6):114–19. Doi: 10.46234/Ccdcw2021.030

[32] Djangwani J, Ooko Abong' G, Gicuku Njue L, Kaindi Dwm. Brucellosis. Prevalence With Reference To East African Community Countries - A Rapid Review. Veterinary Medicine And Science. 2021;7(3):851-867. Doi: 10.1002/Vms3.425.

[33] Holt Hr, Bedi Js, Kaur P, Mangtani P, Sharma Ns, Gill Jps, Singh Y, Kumar R, Kaur M, Mcgiven J, Guitian J. Epidemiology Of Brucellosis In Cattle And Dairy Farmers Of Rural Ludhiana, Punjab. Plos Neglected Tropical Diseases. 2021; 15(3): E0009102. Https://Doi.Org/10.1371/Journal.Pntd.0009102.

[34] Mangalgi S S, Sajjan A G, Mohite S T, And Kakade S V. Serological, Clinical, And Epidemiological Profile Of Human Brucellosis In Rural India. Indian Journal Of Community Medicine. 2015;40, 163–167. Doi: 10.4103/0970-0218.158847

[35] Shome R, Kalleshamurthy T, Shankaranarayana Pb, Giribattanvar P, Chandrashekar N, Mohandoss N, Shome Br, Kumar A, Barbuddhe Sb, Rahman H. Prevalence And Risk Factors Of Brucellosis Among Veterinary Health Care Professionals. Pathogens And Global Health. 2017;111(5):234-239. Doi: 10.1080/20477724.2017.1345366.

[36] Jamir T, Laskar S A, Sarma V, And Deka N N. Brucellosis In Patients With Pyrexia Of Unknown Origin In Assam, India: A Retrospective Record Review. Lancet Global. 2020; 8: S28. Doi: 10.1016/S2214-109x (20)30169-8

[37] Mangtani P, Berry I, Beauvais W, Holt Hr, Kulashri A, Bharti S, Sagar V, Nguipdop-Djomo P, Bedi J, Kaur M, Guitian J, Mcgiven J, Kaur P, Singh Gill Jp, Grover Gs, Kumar R. The Prevalence And Risk Factors For Human Brucella Species Infection In A Cross-Sectional Survey Of A Rural Population In Punjab, India. Transactions Of The Royal Society Of Tropical Medicine And Hygiene. 2020;14(4):255-263. Doi: 10.1093/Trstmh/Trz133. Pmid: 32086527.

[38] Ghugey S L, Setia M S, And Deshmukh J S. Human Brucellosis: Seroprevalence And Associated Exposure Factors Among The Rural Population In Nagpur, Maharashtra, India. Journal Of Family Medicine And Primary Care. 2021;10: 1028–1033. Doi: 10.4103/Jfmpc.Jfmpc_1153_20

[39] Priyadarshini A, Sarangi L N, Palai T K, Panda H K, Mishra R, And Behera P C. Brucellosis In Cattle And Occupationally Exposed Human Beings: A Serosurvey In Odisha India. Journal Of Pure And Applied Microbiology.2013;7(4):3255-3260

[40] Chand P, Chhabra R. Herd And Individual Animal Prevalence Of Bovine Brucellosis With Associated Risk Factors On Dairy Farms In Haryana And Punjab In India. Tropical Animal Health And Production. 2013; 45: 1313–9. Https://Doi.Org/10.1007/S11250-013-0362-Y

[41] Ul-Islam, M R, Gupta M P, Gursimran F, Sidhu P K, Shafi T A, Bhat S A, Hussain, S A & Radya M. Sero-Epidemiology Of Brucellosis In Organized Cattle And Buffaloes In Punjab (India). Advances In Animal And Veterinary Sciences. 2013; 1(3s): 5–8.

[42] Dhand Nk, Gumber S, Singh Bb, Aradhana, Bali Ms, Kumar H, Sharma Dr, Singh J, Sandhu Ks. A Study On The Epidemiology Of Brucellosis In Punjab (India) Using Survey Toolbox. Revue Scientifique Et Technique. 2005; (3):879-885.

[43] Ali S, Nawaz Z, Akhtar A, Aslam R, Zahoor Ma: Ashraf, M. Epidemiological Investigation Of Human Brucellosis In Pakistan. Jundishapur Journal Of Microbiology. 2018; 11: 61764.

[44] Ali S, Ali Q, Neubauer H, Melzer F, Elschner M, Khan I, Abatih En, Ullah N, Irfan M, Akhter S. Seroprevalence And Risk Factors Associated With Brucellosis As A Professional Hazard In Pakistan. Foodborne Pathogens And Diseases. 2013, 6: 500–05.

[45] Ali S, Akhter S, Neubauer H, Scherag A, Kesselmeier M, Melzer F, Khan I, El-Adawy H, Azam A, Qadeer S, Ali Q. Brucellosis In Pregnant Women From Pakistan: An Observational Study. Bmc Infectious Diseases. 2016;16(1):468. Doi: 10.1186/S12879-016-1799-1.

[46] Shukla J L, Husain A, Nayak A R, Bhartiya N, Daginawala H, Singh L, & Kashyap R S. Seroprevalence And Associated Risk Factors Of Human Brucellosis From A Tertiary Care Hospital Setting In Central India. Journal Of Zoonotic Diseases. 2020;4(4): 9-20. Doi: 10.22034/Jzd.2020.11600

[47] Dutta D, Sen A, Gupta D, Kuila P, Chatterjee D, Sanyal S & Das S: Childhood Brucellosis In Eastern India. Indian Journalof Pediatrics 2018;85: 266–71. Https://Doi.Org/10.1007/S12098-017-2513-Z

[48] Mantur Bg, Amarnath Sk, Shinde Rs. Review Of Clinical And Laboratory Features Of Human Brucellosis. Indian Journal Of Medical Microbiology. 2007; 25: 188–202. Https://Doi.Org/10.1016/S0255-0857(21)02105-8

[49] Modak D, Biswas S, Mondal A, Biswas M, Mascellino Mt, Chakraborty B, Tiwari S, Shewale Ad, Nale T, Dey R. Seroprevalence Of Brucellosis Among Animal Handlers In West Bengal, India: An Occupational Health Study. Aims Microbiology. 2024;10(1):1-11. Doi: 10.3934/Microbiol.2024001.

[50] Al-Anaz, Ka & Al-Jasser Am. Brucella Bacteremia In Patients With Acute Leukemia: A Case Series. Journal Of Medical Case Reports . 2007; 1: 144. Https://Doi.Org/10.1186/1752 1947-1-144

[51] Uzunović S, Skomorac M, Bašić F, Kamberović F, Ibrahimagić A, And Dizdarević J. Human Brucellosis As An Epidemic Zoonosis In Zenica-Doboj Canton (Bosnia And Herzegovina) During 2008–2018. Open Infectious Diseases Journal. 2020;12(1):1–6. Doi: 10.2174/18742793020 12010001.

[52] Bennett Nj. Brucellosis. Medscape; 2023. Available From: Https://Emedicine.Medscape.Com/Article/213430- Overview?Form=Fpf

[53] Makita K, Fevre Em, Waiswa C, Kaboyo W, Bronsvoort Bmdc, Eisler Mc & Wellburn Sc: Human Brucellosis In Urban And Peri-Urban Areas Of Kampala, Uganda. Annals Of New York Academy Sciences. 2008,1149: 309-311. Https://Doi.Org/10.1196/Annals.1428.015.

[54] Lapaque N, Forquet F, De Chastellier C, Mishal Z, Jolly G& Moreno E, Moriyon I,Heuser Je, He Hai-Tao Gorvel Jp. Characterization Of Brucella Abortuslipopolysaccharide Macrodomains As Mega Rafts. Cell Microbiology 2006;8 (2):197-206

[55] Arlett Pr: A Case Of Laboratory Acquired Brucellosis. Bmj 1996, 313:1130-2.

[56] Yagupsky P, Baron Ej. Laboratory Exposures To Brucellae And Implications For Bioterrorism. Emerg Infect Dis. 2005,11:1180 5.

[57] Williams E: Brucellosis And The British Public. Lancet 1970; 1:1220-1222.

[58] Pappas G, Akritidis N, Bosilkovski M & Tsianos E.Brucellosis. The New England Journal Of Medicine 2005; 352:2325-2336. Https://Doi.Org/10.1056/Nejmra050570

[59] Pandit Dp, Pandit Pt. Human Brucellosis: Are We Neglecting An Enemy At The Backyard? Medical Journal Of Dr. Dy Patil University.2013; 350: 8. Https://Doi.Org/10.4103/0975-2870.118265

[60] Godfroid J, Nielsen K & Saegerman C: Diagnosis Ofbrucellosis In Livestock And Wildlife. Cm J. 2010, 51: 296-05. Https://Doi.Org/10.3325/Cmj.2010.51.296

[61] Vigeant P, Mendelson J & Miller M A. Human To Human Transmission Of Brucella Melitensis. Canadian Journal Of Infectious. Diseases. 1995;6: 153–55. Https://Doi.Org/10.1155/1995/909404.

[62] Singh J, Bb Singh, Hk Tiwari, Hs Josan, N Jaswal, M Kaur, P Kostoulas, M S Khatkar Rs Aulakh, Jps Gill. Using Dairy Value Chains To Identify Production Constraints And Biosecurity Risks, Animals.2020; 10: (12) 2332.

[63] Malik Gm: A Clinical Study Of Brucellosis In Adults In The Asir Region Of Southern Saudi Arabia. The American Journal Of Tropical Medicine And Hygiene. 1997; 56:375-377

[64] Godfroid J, Cloeckaert A, Liautard Jp, Kohler S, Fretin D, Walravens K, Garin-Bastuji B, Letesson Jj. From The Discovery Of The Malta Fever's Agent To The Discovery Of A Marine Mammal Reservoir, Brucellosis Has Continuously Been A Re-Emerging Zoonosis. Vetrinary Research. 2005; 36(3):313-326. Doi: 10.1051/Vetres:2005003.

[65] World Health Organization. Brucellosis In Humans And Animals. Produced By The World Health Organization In Collaboration With The Food And Agriculture Organization Of The United Nations (Fao) And World Organisation For Animal Health (Oie); 2006.

[66] Who. Anonymous. Joint Fao/Who Expert Committee On Brucellosis. 4th Rep. Geneva: World Health Organization; 1964.

[67] Kutlu M, Ergonul O, Sayin-Kutlu S, Guven T, Ustun C, Alp-Cavus S, Ozturk Se B, Acicbe O, Akalin S, Tekin R, Tekin-Koruk S, Demiroglu Y Z, Keskiner R, Gönen I, Sapmaz-Karabag S, Bosnak V, Kazak E. Risk Factors For Occupational Brucellosis Among

Veterinary Personnel In Turkey, Journal Of Preventive Veterinary Medicine. 2014;117:(1)52-58, Issn 0167-5877, Https:// Doi.Org/ 10.1016/ J.Pre Vet Med. 2014.07.010.
[68] Memish Z. Brucellosis Control In Saudi Arabia: Prospects And Challenges. Journal Of Chemotherapy. 2001;13:(L) Ll-17.
[69] Young Ej. Brucella Species. In: Mandell Gl, Bennett Je, Dolin R. Eds: Principles And Practice Of Infectious Diseases, Vol. 2. Philadelphia: Churchill Livingstone, 2000;2386- 2392.
[70] Byndloss Mx, Tsolis Rm. Brucella Spp. Virulence Factors And Immunity. The Annual Review Of Animal Biosciences. 2016;4(1):111-27. Doi: 10.1146/Annurev-Animal-021815-111326.
[71] Głowacka P, Żakowska D, Naylor K, Niemcewicz M, Bielawska-Drózd A. Brucella - Virulence Factors, Pathogenesis And Treatment. Polish Journal Of Microbiology. 2018;30;67(2):151-161. Doi: 10.21307/Pjm-2018-029.
[72] Roop R M, Barton I S, Hopersberger D & Martin D. Uncovering The Hidden Credentials Of Brucella Virulence. Microbiology And Molecular Biology Reviews 2021;85:(1), 10-1128.
[73] Ackermann Mr, Cheville Nf, Deyoe Bl. Bovine Ileal Dome Lymphoepithelial Cells: Endocytosis And Transport Of Brucella Abortus Strain 19. Veterinary Pathology 1988;25(1):28–35. Doi:10.1177/030098588802500104
[74] Cosford Kl. Brucella Canis: An Update On Research And Clinical Management. Canadian Veterinary Journal. 2018;59(1):74–81.
[75] Gorvel Jp, Moreno E. Brucella Intracellular Life: From Invasion To Intracellular Replication. Veterinary Microbiology 2002;90(14):281–297. Doi:10.1016/S0378-1135(02)00214-6
[76] Araya In, Elzer P, Rowge, Enright Fm, Winter J. Temporal Development Of Protective Cell Mediated Immunity & Humoral Immunity In Balb / Cmice Infected With Brucella Abortus In J 774 Macrophages. Infection And Immunity. 1989; 143:3330-3337.
[77] Sangari Fj, Seoane A, Rodriguez Mc, Aguero J, Garcia Lobo Jm.Characterization Of The Urease Operon Of Brucella Abortus And Assessment Of Its Role In Virulence Of The Bacterium. Infection And Immunity. 2007; 75:774-780
[78] Trujillo Iz, Zavala An, Caceres Jg, Miranda Cq. Brucellosis. Infectious Disease Clinics Of North America.1994; 8:225-241.
[79] Young Ej. Brucellosis. In: Emmerson Am, Hawkey Pm, Gillespie Sh. Eds Principles And Practice Of Clinical Bacteriology. Chichester: Wiley, 1997;337-348.
[80] Maduranga S, Valencia Bm, Li X, Moallemi S & Rodrigo C. A Systematic Review And Meta-Analysis Of Comparative Clinical Studies On Antibiotic Treatment Of Brucellosis. Scientific Reports .2024; 14: 19037. Https://Doi.Org/10.1038/S41598-024-69669-W
[81] Galinska Em, Zagórski J. Brucellosis In Humans-Etiology, Diagnostics, Clinical Forms. Annals Of Agricultural And Environmental Medicine . 2013; 20: 233–238.
[82] Li Q, Liu J, Jiang W, Jiang L, Lu M, Xiao L, Li Y, Lan Y & Li Y. A Case Of Brucellosis-Induced Guillain–Barre Syndrome. Bmc Infectious Diseases. 2022;22(1):72. Doi: 10.1186/S12879-021-07025-3.
[83] Essrani R, Shnitser A. Brucella Melitensis-Induced Trans Aminitis. Cureus. 2021;13(3): E13656. Doi: 10.7759/Cu Reus.13656.
[84] Kaya F, Kocyigit A, Kaya C, Turkcuer I, Serinken M, Karabulut N. Brucellar Testicular Abscess Presenting As A Testicular Mass: Can Color Doppler Sonography Be Used In Differentiation? Turkish Journalof Emergency Medicine 2016;15(1):43-46. Doi: 10.5505/1304.7361.2014.82698.
[85] Wang W, Lu X, Li C, Jun M & Cui W. A Man With Recurrent Fever, Arthritis, And Rashes—Brucellosis? A Case Reports. Bmc Infectious Diseases. 2020;20(1):18. Doi: 10.1186/S12879-019-4746-0.
[86] Wareth G, Melzer F, Neubauer H. In Brucella: Selective Pressure May Turn Some Genes On Instead Of Default Off Position. Medical Hypotheses. 2017; 103:29–31. Doi: 10.1016/J.Mehy.2017.04.006
[87] Qureshi K A, Adil Parvez, Nada A. Fahmy, Bassant H. Abdel Hady, Shweta Kumar, Anusmita Ganguly, Akhtar Atiya, Gamal O. Elhassan, Saeed O. Alfadly, Seppo Parkkila & Ashok Aspatwar: Brucellosis: Epidemiology, Pathogenesis, Diagnosis And Treatment–A Comprehensive Review, Annals Of Medicine. 2023; 55:2, 2295398, Doi: 10.1080/07853890.2023.2295398
[88] Al-Attas Ra, Al-Khalifa M, Al-Qurashi Ar, Badawy M, Al-Gualy N. Evaluation Of Pcr, Culture And Serology For The Diagnosis Of Acute Human Brucellosis. Annals Of Saudi Medicine. 2000; (3-4):224-8. Doi: 10.5144/0256-4947.2000.224.
[89] Wareth G, Pletz Mw, Neubauer H, Murugaiyan J. Proteomics Of Brucella: Technologies And Their Applications For Basic Research And Medical Microbiology. Microorganisms. 2020; 8(5):766. Https://Doi.Org/10.3390/Microorganisms8050766
[90] Di Bonaventura G, Angeletti S, Ianni A, Petitti T, Gherardi G. Microbiological Laboratory Diagnosis Of Human Brucellosis: An Overview. Pathogens. 2021; (12):1623. Doi: 10.3390/Pathogens10121623.
[91] El-Diasty M, El-Said R, Abdelkhalek A. Seroprevalence And Molecular Diagnosis Of Sheep Brucellosis In Dakahlia Governorate, Egypt. German Journal Of Veterinary Research. 2021;1(1):34–39. Doi: 10.51585/Gjvr.2021.0006.
[92] Saeed U, Ali S, Khan Tm, El-Adawy H, Melzer F, Khan Au, Iftikhar A & Neubauer H; Seroepidemiology And The Molecular Detection Of Animal Brucellosis In Punjab, Pakistan. Microorganisms. 2019; 7: 449. Https://Doi.Org/ 10.3390/Microorganisms7100449
[93] Mantecón Má, Gutiérrez P, Del Pilar Zarzosa, M, Duenas Ai, Solera J & Fernández-Lago L. Utility Of An Immunocapture-Agglutination Test And Anenzyme-Linked Immunosorbent Assay Test Against Cytosolic Proteins From Brucella Melitensis B115 In The Diagnosis And Follow-Up Of Human Acute Brucellosis. Diagnostic Microbiology And Infectious Disease. 2006;55: 27-35. Https://Doi.Org/10.1016/ J.Diagmicrobio.
[94] Al-Shamahy Ha, Wright Sg. Enzyme-Linked Immunosorbent Assay For Brucella Antigen Detection In Human Sera. Journal Of Medical Microbiology. 1998; 47:169-172.
[95] Jamil T, Melzer F, Njeru J, El-Adawy H, Neubauer H, Wareth G. Brucella Abortus: Current Research And Future Trends. Current Clinical Microbiology Reports. 2017; 4: 1–10.
[96] Li M, Zhou X, Li J, Sun L, Chen X, Wang P. Real-Time Pcr Assays For Diagnosing Brucellar Spondylitis Using Formalin-Fixed Paraffin-Embedded Tissues. Medicine (Baltimore). 2018; (9): E0062. Doi: 10.1097/Md.0000000000010062.
[97] Dean As, Crump L, Greter H, Schelling E, Zinsstag J. (2012) Global Burden Of Human Brucellosis: A Systematic Review Of Disease Frequency. Plos Neglected Tropical Diseases 2012; 6(10): E1865. Doi: 10.1371/Journal.Pntd.0001865
[98] Mor Sm, Wiethoelter Ak, Massey Pd, Robson J, Wilks K, Hutchinson P. Pigs, Pooches And Pasteurisation: The Changing Face Of Brucellosis In Australia. Australian Journal Of General Practice. 2018;47(3):99-103. Doi: 10.31128/Afp-08-17-4289. Pmid: 29621840.
[99] Solera J. Update On Brucellosis: Terapeutic Challenges. International Journal Of Antimicrobial Agents. 010, 36, S18–S20. Https://Doi.Org/10.1016/J.Ijantimicag.2010.06.015.
[100] Ariza J, Corredoira J, Pallares R, Viladrich Pf, Rufi G, Pujol M, Gudiol F. Characteristics Of And Risk Factors For Relapse Of Brucellosis In Humans. Clinical Infectious Diseases. 1995;20(5):1241-1249. Doi: 10.1093/Clinids/20.5.1241. Pmid: 7620005.
[101] World Health Organization. Joint Fao/Who Expert Committee On Brucellosis. Sixth Report. World Health Organ Tech Rep Ser No. 740. World Health Organization: Geneva; 1986.

[102] Doganay M, Bilgehan A. Human Brucellosis: An Overview, International Journal Of Infectious Diseases. 2003;7: 173-182, Issn 1201-9712, Https://Doi.Org/10.1016/S1201-9712(03)90049-X.
[103] Silva Sn, Cota G, Xavier Dm, De Souza Gm, Souza Mrf, Goncalves Mwa Tuon Ff, Galvão El: Efficacy And Safety Of Therapeutic Strategies For Human Brucellosis: A Systematic Review And Network Meta-Analysis. Plos Neglected Tropical Diseases 2024; 18(3): E0012010. Https://Doi.Org/10.1371/Journal. Pntd.0012010
[104] Bosilkovski M, Edwards Ms, Calderwood Sb: Brucellosis: Epidemiology, Microbiology, Clinical Manifestations, And Diagnosis. Up To Date, United States. 2019.
[105] Ozbay K, Inanmis Ra. Successful Treatment Of Brucellosis In A Twin Pregnancy. Clinical And Experimental Obstetrics & Gynecology. 2006; 33:61-62
[106] Centers For Disease Control And Prevention. Treatment. Brucellosis. Cdc: 2012. Available From: Https://Www. Cdc.Gov/Brucellosis/Treatment/Index.Html
[107] Yuan W, Zhang M, Zou H, Gao X, Luan Y. Emergency Response To Occupational Brucellosis In A Pharmaceutical Manufacturing Enterprise. Journal Of Occupational Health. 2018;60(5):404 409. Doi: 10.1539/Joh.2018-0089-Cs.
[108] A Etemadi, Rezvan M, Mahmoods, Hossein A, Saeed A, Ali Mohammad B. Epidemiological, Molecular Characterization And Risk Factors Of Human Brucellosis In Iran. Asian Pacific Journal Of Tropical Medicine.2020; 13(4): P 169-175, Doi: 10.4103/1995-7645.280224.
[109] Heidary M, Dashtbin S, Ghanavati R, Mahdizade Ari M, Bostanghadiri N, Darbandi A, Navidifar T And Talebi M. Evaluation Of Brucellosis Vaccines: A Comprehensive Review. Frontiers In Veterinary Science. 2022; 9:925773. Doi: 10.3389/ Fvets. 2022. 925773
[110] Mansoori N, Pourmand Mr.Vaccines And Vaccine Candidates Against Brucellosis. Infection, Epidemiology And Microbiology. 2016; 2(4):32–36. Doi: 10.18869/Modares.Iem.2.4.32.
[111] Montaraz Ja, Winter Aj. Comparison Of Living And Non-Living Vaccines For Brucella Abortus In Balb/C Mice. Infection And Immunity. 1986;53(2):245–251. Doi: 10.1128/ Iai.53.2.245-251.1986.
[112] Nicoletti P. Control, Eradication And Prevention. In: Madkour Mm, Editor. Madkours Brucellosis. Springer: New York; 2001. P. 280-285.
[113] Madkour Mm. Epidemiologic Aspects. In: Madkour Mm, Editor. Madkour S Brucellosis. Springer: New York; 2001, P. 21-32.