



OVERVIEW OF BRUCELLOSIS: SIMPLE REVIEW ARTICLE

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ABSTRACT

In the majority of the developing ecosphere, brucellosis is an endemic zoonotic disease that has devastating effects on the livestock industry and small-scale cattle owners. Clinical symptoms displayed by infected animals have an economic impact on stakeholders. These include a significant decline in milk manufacturing, reduced fertility, abortion, poor weight gain, losses in the drawing power, and poor weight gain. Brucellosis commonly presents in people as a range of non-specific clinical symptoms. Brucella infections can damage any organ or bodily system and lead to a range of focal issues and clinical situations, despite the fact that brucellosis in humans often presents as a feverish condition with no obvious focus, either from the outset of the disease or during its course. Unfortunately, only a small number of these potential settings—primarily infections brought on by *B. melitensis*—have received enough research into the diagnostic yield of NAATs. Due to these restrictions, we will concentrate on the clinical conditions with the strongest body of data.

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Introduction

The bacterium genus *brucella* is responsible for the mutual zoonotic illness known as brucellosis. An ancient illness called brucellosis is sometimes known as Mediterranean fever or undulant fever. One of the infectious illnesses that may spread from animals to people is this one. Some ways for the *Brucella* bacteria to proliferate within the body include ingesting, surviving, coming into touch with injured skin, and smuggling foetuses or amniotic fluid from sick animals [1]. The Mediterranean region, the southern and central regions of America, Africa, Asia, the Arab peninsula, the Indian subcontinent, and the Middle East are all regions where this sickness is more contagious. Fever, night sweats, asthenia, sleeplessness, anorexia, and headache are the most typical nonspecific signs of brucellosis [2].

Medical symptoms of infection in diseased animals comprise reduced fertility, abortion, poor bulk advance, loss breeze regulation, and a significantly flagging decrease in milk output. These clinical indicators have economic significance to stakeholders [3].

The primary issue in endemic areas is brucellosis control. Controlling the animal illness and closing the door on human transmission are the only ways to halt human brucellosis. A limited number of rich nations have successfully controlled or even eradicated brucellosis through extensive and expensive animal vaccination programmes that were then followed by the killing of sick animals who were already well along in the disease's progression. To avoid human illnesses, proper food hygiene is crucial, notably the sterilisation of milk [4]. Change of a disease like brucellosis requires a "One Health" strategy. To inform and educate the population at risk, animal and human well-being must collaborate with livestock owners and programmes that are well-known. It is crucial that political decision makers have a significant role. If it hasn't already been done, monitoring local residents, both human and animal, is a good idea [5].

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Particularly *B. melitensis*, *B. abortus*, and *B. suis*, *Brucella* spp. represent a serious public health issue. *B. melitensis* is currently the main cause of human brucellosis in India. The evolutionary relationship between *Brucella* and *Agrobacterium*, *Ochrobactrum*, and *Rhizobium* has been confirmed by molecular research. Hominid brucellosis continues to provide a number of challenges for researchers and medical professionals in terms of understanding its pathogenic process, rigorousness, evolution, and extension of better management schedules [6]. In order to provide novel analytical methods that would be helpful in developing nations where brucellosis is a widespread, but frequently neglected illness, molecular researches have recently outlined the pathophysiology of *Brucella* [6].

Cattle, dogs, sheep, goats, and pigs are the shared reservoirs for *Brucella* germs that might communicate a disease to humans. Though brucellosis may exist anywhere, it has primarily afflicted the Mediterranean region. Straight or accidental interaction through wildlife, consumption of polluted animal yields (including raw milk besides dairy produces) or breath of vaporizers is the three main ways that humans get an infection [1].

After five to sixty days of incubation, symptoms may start to show either suddenly or slowly. In its raw state, the illness can progress to chronicity. Both general (fever, weakness, joint pain) and organ-specific symptoms are among the different indicators (with infections in the brain contagion and heart valves). Brucellosis can be fatal if left untreated [7].

Long-term antibiotic therapy often works. Animal immunisation, test-and-kill procedures for sick animals, processing of milk and dairy products are all examples of control techniques [8].

Human brucellosis seldom results in death, although it can cause simple impairment and debilitation. Nevertheless, it is stated that 2% of the patients with crude die from brucellosis. The condition has a propensity to be chronic and persistent, drawing a granulomatous illness that can impact any organ system [9].

Epidemiology of Brucellosis

Brucella can't be detected by all equipment, but MALDI-TOF mass spectrometry is revolutionising the clinical diagnostic workroom. We created a spectrum file that enabled the bioMérieux VITEK organisation to identify *Brucella* [9] and a secure, efficient technique for solvent inactivation prior to analysis. Solvent-incapable bacteria can be transported to a facility with an instrument since they are stable for several days [10]. In the current ecosphere, molecular epidemiology uses multilocus sequence typing (MLST) and multiple-locus adjustable number tandem repeat examination (MLVA). These investigations, which will be important in upcoming control initiatives, demonstrate how *B. melitensis* and *B. abortus* strains have persisted in being traded as animals all over the world. MLST and MLVA education employing full whole-genome orders will be automated and generalised as a result of developments in sequencing technology, according to the epidemiology of brucellosis [11].

Brucellosis Pathogenicity

Similar to extra intracellular pathogens, *Brucella* spp. are facultative intracellular germs that have the capacity to avoid the killing process and grow within the macrophages. *Brucella* requires four processes to be an effective infectious agent: dedication, invasion, establishment, and dispersion within the host. *Brucella*, both opsonized and unopsonized, can infect macrophages. so simulating direct host cell contact, which permits adhesion and invasion as well as phagocytizations mediated by antibodies or companion cells. inside macrophages. *Brucella* lockups persist and proliferate, preventing the formation of phagosome-lysosomes. The accumulating bacteria are finally isolated from the other host cells [6].

The pathogen infects the host and renovates trapped confidential to the reticuloendothelial system's cells. Numerous studies and discussions have been conducted on the method by which *Brucella* penetrates the prison cell and escapes intracellular destruction and the host immune system [12].

Pathophysiology of Brucellosis

Humans may get the zoonotic disease brucellosis through eating undercooked meat or raw dairy products, inhaling the bacteria, or by the bacterium coming into direct contact with skin wounds or mucous membranes. Next episode White blood cells then phagocyte the pathogen and transport it to other organs, especially those with the reticulo-endothelial system, via the hematologic or lymphatic pathway [13]. Endotoxic lipopolysaccharide LPS has a significant impact on how long microorganisms may survive inside monocytic cells, how phagosome-lysosome fusion is suppressed, and how bacteria enter the endoplasmic reticulum. The following stages can be used to identify the pathophysiology of Brucellosis [14].

It takes 10–100 communicable germs to infect the body systemically. Three basic phases can be identified when the creature enters: the incubation period, acute point, and chronic phase [15].

The conception time of brucellosis could vary besides it is difficult to predict, although it typically lasts between 2 and 4 weeks, also could vary from five days to five months. The emergence of symptoms and signs such fever, sweating, tiredness, hepatomegaly, and splenomegaly are what define the serious phase [16].

Brucella may persist in host cells and avoid host immune responses to establish chronic emphases of infection due to a number of virulence influences [12].

Diagnosis of Brucellosis

Brucellosis may have been contracted by people for the first time soon after cattle, camels, sheep, goats, and swine were domesticated. Humans signify the disease's final point. Eliminating the microbe from cattle is essential for averting human

toxicity since brucellosis is not a sustained illness in people and is almost continuously spread to humans thru straight or unintended contact with diseased animals or feasting of their polluted produces [17].

Blood cultures in tryptose broth and bone marrow cultures are used in the diagnosis of brucellosis. Due to the brucellae's high contagiousness and extremely sluggish development rate (they can take up to two months to mature), workshop workers are at danger. ELISA or the 2-mercaptoethanol test for IgM antibodies associated with chronic disease can detect antibodies against the agent with the characteristic Huddleson, Wright, and/or Bengal Rose responses [18].

The mainstay of brucellosis diagnostic techniques is serology, with the LPS smooth chains inducing the strongest immune responses in different hosts. Due to similarities between the O-antigenic side chain of Brucella's LPS and those of Yersinia enterocolitica O: 9, Vibrio cholerae, Escherichia coli O: 157, and Francisella tularensis, the main diagnostic challenge arises. However, these have mainly been ineffective. Other antigens have been tested for their analytical potential and for a potential improvement in their specificity. In the investigation of bacterial illnesses, including brucellosis, blood culture is the gold standard [19].

Because human brucellosis can affect any organ or system of the body, its pathognomonic symptoms are not always present, making it possible for the disease to be mistaken for other illnesses. On the other hand, a brucellosis overdiagnosis may lead to unwanted treatment side effects and, just as seriously, to the neglect of more significant infectious or non-infectious disorders. In addition to being difficult, treating brucellar infections with antibiotics requires prolonged administration of antimicrobial medication combinations that are not often prescribed for other communicable illnesses [20].

Therefore, a proper diagnosis of brucellosis in humans is essential for prompt and effective patient care as well as having important public health implications as it may show exposure to ill animals, consumption of contaminated food (particularly dairy products), break of factory protection prepares, or the deliberate proclamation of brucellae as a organic canister [18].

Viewpoint, serology, and nucleic acid firming examinations are three distinct categories used in the bacteriological judgment of humanoid brucellosis (NAATs). This analysis presents a computation of the comparative benefits in addition to downsides of the diagnostic techniques' current ranking, medical use, and new improvements [21, 22].

Laboratory Diagnosis

Tests for agglutination, such as the Rose Bengal test, serum cohesion test, antiglobulin or Coombs test, complement fixation test, and the only just introduced immunocapture examination, are used in laboratories to diagnose brucellosis when a culture is absent. The serum agglutination tests are used to confirm positive results from the Rose Bengal examination, that is used for instance a broadcast test [23]. This agglutination test was developed using antibodies that react negatively to smooth lipopolysaccharide. The sensitivity of the Rose Bengal Plate (RBPT) agglutination test is great (>99 percent), and erroneous negative outcomes are seldom seen. The test may be used with repeated dilutions of blood samples (1:2 through 1:64) to improve specificity. The greatest widely used and simple test is the Regular Tube Agglutination Test (SAT), which was created by Wright and colleagues. The total amount of the agglutinating antibodies may be determined by SAT (IgG and IgM). The serum is treated with 0.005M 2 mercaptoethanol (2ME), which neutralises the IgM's capacity to agglutinate, to increase the amount of specific IgG [24].

Blood Examination for Brucellosis

To regulate the seroprevalence of brucellosis, two different serological assays were performed. Rose Bengal Plate Test (RBPT) was used to screen the sera, and ELISA was also performed on positive samples. In the Addis Ababa Federal police workshop, all sera, RBPT reagents, and wheels were removed from the refrigerator and maintained at room temperature for 30 minutes to be tested for anti-Brucella antibodies. The smooth attenuated marked Brucella antigen solution was combined with positive and negative controls, serum, and a round test card as previously labelled. If the serum contains a particular anti-Brucella antibody, shaking it for four minutes at low speed will cause observable agglutination as a result of the antigen delay. A lack of agglutination means that a nonappearance of precise antibodies to Brucella antigens [25].

In comparison thru conventional tests like circular immunodiffusion (RID), complement fixation (CF), rose bengal agglutination (RB), in addition to rivanol agglutination (RV), two unintended and two diffident Enzyme-linked immunosorbent assays (I-ELISA102, IELISA103, C-ELISA1, and C-ELISA2 respectively) have been assessed [26]. The Joint FAO/IAEA Partition, Vienna, Austria, provided all the ELISA targets, their methods, and computer analyses, which were all carried out as detailed in earlier studies. The conventional serological tests were carried out as reported elsewhere and industrialised. The sera tested comprised 665 from B. abortus biotype 1 (field strain)-infected individuals, 848 from brucellosis-free masses calf vaccinated with Strain-19, 295 from brucellosis-free herds adult vaccinated with Strain-19, and 1018 from nonvaccinated bovines [27].

Risk Factors of Brucellosis

Risk factors for the illness spreading inside animals include age, the practice of transhumance, herd size, and the frequency of abortions. These risk variables have to do with the intricate relationships between and within the various production systems as well as the various behaviors seen in urban, periurban, and rural locations [28].

Treatment of Brucellosis

Treatment for brucellosis is to manage the condition and avoid complications, reverts, side effects, then death. Administering of antibiotics thru act in acidic intracellular situations (such as doxycycline and rifampin), the use of combination therapy (given the high recurrence rates with monotherapy), and prolonged length of managing are universal ideologies of brucellosis comportment [29, 30].

The standard treatment for brucellosis is double therapy thru doxycycline and gentamicin. Doxycycline oral treatment is required for six weeks, with daily intravenous gentamicin as an adjuvant meant for the chief 7 days period [31, 32].

The risk of treatment failure and degeneration is reduced by gentamicin, but it has the potential to cause substantial renal, vestibular, and ototoxicity, necessitating specialised helpful medication observing and hospital prices [33].

Issues related to the treatment of brucellosis in the absence of focal sickness due to spondylitis, neurobrucellosis, or endocarditis are discussed in the section under. These routines are used for the treatment of osteoarticular disease in the nonappearance of spondylitis (such as sacroiliitis, and peripheral arthritis), as fine as for management of other forms of the focal disease (such as genitourinary assembly, and pulmonary participation [34].

Though some studies have pointed to several risk factors for management failure or relapse, the best treatment regimen has not been gritty. The effectiveness of the different regimens in special situations such as pregnancy, chronic brucellosis, complicated suitcases, immunocompromised patients, or dialysis is related to the different results. The use of other medications such as gentamicin, quinolones, and cotrimoxazole (CTM) either alone or as a mixture with other medications has been associated with different consequences [35].

Plants Used in Treating Brucellosis

Even though antibiotic therapy remains the primary method for treating serious brucellosis in hominids [36], usage of medical plants has grown among adults and children in recent years, to the point where almost 4 out of every 10 Americans now turn to non-conventional treatment methods like therapeutic plants. Plants form more than one-third of chemical pharmaceuticals, and there is a great potential for using them to make medicines that are even more strong. Therapeutic plants are used to treat a variety of illnesses, including bacterial infections, cancer, musculoskeletal disorders, acquired immune deficiency syndrome, and depression. Due to limited resistance to high fevers and the carcinogenicity of some synthetic substances, the usage of common antioxidants has recently received attention [37, 38].

Control of Brucellosis

The primary problem in vast regions is brucellosis controlling. Controlling the animal illness and closing the door on human transmission are the lone ways toward controlling human brucellosis. A limited number of affluent nations have successfully eliminated brucellosis through extensive and expensive animal immunisation programmes, trailed thru the slaughter of sick animals as they progressed. To avoid human illnesses, food safety is crucial, specifically when it comes to sterilising milk [39, 40].

The transition of a infection like brucellosis necessitates a "One Health" strategy. In order to notify and instruct the community at threat, bodily and human health professionals must collaborate through the livestock owners and packaging identified. Party-political decision-makers must be strongly implied. The investigation of people and other living things ought to be implemented, if it hasn't already [41].

Decent vaccinations are required for vaccination campaigns. Ended the earlier few years, two live vaccines, *B. melitensis* Rev. 1 and *B. abortus* S19, have been used to remarkable success aimed at small ruminant besides bovine brucellosis management programmes globally. Additionally, *B. abortus* RB51 is recommended as an inoculation for bovine brucellosis to be used in combination through checking in addition to assassination in the ultimate phases of control programmes [42].

Conclusion

In low-, middle-, and high-income nations, brucellosis is a common zoonotic illness that has a severe impact on the cattle trade, particularly small-scale beef producers. It significantly increases the costs of humanoid health services programmes and reduces the financial impending of people, societies, and nations when this growing is crucial to reducing the incidence of insufficiency. It is urgently necessary to develop civic policies aimed at reducing the economic effects of brucellosis in both humanoid in addition to animal residents.

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References

1. Alton GG, Forsyth JRL. Brucella. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 28. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK8572/>
2. Bagheri Nejad R, Krecek RC, Khalaf OH, Hailat N, Arenas-Gamboia AM. Brucellosis in the Middle East: Current situation and a pathway forward. *PLoS Negl Trop Dis*. 2020;14(5):e0008071. doi:10.1371/journal.pntd.0008071
3. Lefkaditis M, Mpairamoglou R, Sossidou A, Spanoudis K, Tsakiroglou M. Neospora caninum, A potential cause of reproductive failure in dairy cows from Northern Greece. *Vet Parasitol Reg Stud Rep*. 2020;19:100365. doi:10.1016/j.vprsr.2019.100365
4. Moreno E, Blasco JM, Moriyón I. Facing the Human and Animal Brucellosis Conundrums: The Forgotten Lessons. *Microorganisms*. 2022;10(5):942. doi:10.3390/microorganisms10050942
5. Godfroid J. Brucellosis in livestock and wildlife: zoonotic diseases without pandemic potential in need of innovative one health approaches. *Arch Public Health*. 2017;75(1):34. doi:10.1186/s13690-017-0207-7
6. Christopher S, Umapathy BL, Ravikumar KL. Brucellosis: review on the recent trends in pathogenicity and laboratory diagnosis. *J Lab Physicians*. 2010;2(2):55-60. doi:10.4103/0974-2727.72149
7. Park MB, Park EY, Lee TS, Lee J. Effect of the Period From COVID-19 Symptom Onset to Confirmation on Disease Duration: Quantitative Analysis of Publicly Available Patient Data. *J Med Internet Res*. 2021;23(9):e29576. doi:10.2196/29576
8. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. *Molecules*. 2018;23(4):795. doi:10.3390/molecules23040795
9. Byndloss MX, Tsolis RM. Chronic Bacterial Pathogens: Mechanisms of Persistence. *Microbiol Spectr*. 2016;4(2). doi:10.1128/microbiolspec.VMBF-0020-2015
10. Mesureur J, Ranaldi S, Monnin V, Girard V, Arend S, Welker M, et al. A Simple and Safe Protocol for Preparing Brucella Samples for Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry Analysis. *J Clin Microbiol*. 2016;54(2):449-52. doi:10.1128/JCM.02730-15
11. Ma JY, Wang H, Zhang XF, Xu LQ, Hu GY, Jiang H, et al. MLVA and MLST typing of Brucella from Qinghai, China. *Infect Dis Poverty*. 2016;5(1):26. doi:10.1186/s40249-016-0123-z
12. Ahmed W, Zheng K, Liu ZF. Establishment of Chronic Infection: Brucella's Stealth Strategy. *Front Cell Infect Microbiol*. 2016;6:30. doi:10.3389/fcimb.2016.00030
13. Gwida M, Al Dahouk S, Melzer F, Rösler U, Neubauer H, Tomaso H. Brucellosis - regionally emerging zoonotic disease? *Croat Med J*. 2010;51(4):289-95. doi:10.3325/cmj.2010.51.289
14. Porte F, Naroeni A, Ouahrani-Bettache S, Liautard JP. Role of the Brucella suis lipopolysaccharide O antigen in phagosomal genesis and in inhibition of phagosome-lysosome fusion in murine macrophages. *Infect Immun*. 2003;71(3):1481-90. doi:10.1128/IAI.71.3.1481-1490.2003
15. van Seventer JM, Hochberg NS. Principles of Infectious Diseases: Transmission, Diagnosis, Prevention, and Control. *Int Encycl Public Health*. 2017:22-39. doi:10.1016/B978-0-12-803678-5.00516-6
16. Cleri DJ, Ricketti AJ, Vernaleo JR. Fever of unknown origin due to zoonoses. *Infect Dis Clin North Am*. 2007;21(4):963-96. doi:10.1016/j.idc.2007.08.009
17. Spinage CA. Zoonoses Animal and Human Diseases Endo and Ectoparasites Mainly Mammal I. *Afr Ecol*. 2011;1101-49. doi:10.1007/978-3-642-22872-8_23
18. Yagupsky P, Morata P, Colmenero JD. Laboratory Diagnosis of Human Brucellosis. *Clin Microbiol Rev*. 2019;33(1):e00073-19. doi:10.1128/CMR.00073-19
19. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. *N Engl J Med*. 2005;352(22):2325-36. doi:10.1056/NEJMra050570
20. Hayoun MA, Muco E, Shorman M. Brucellosis. [Updated 2022 May 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441831/>
21. Di Bonaventura G, Angeletti S, Ianni A, Petitti T, Gherardi G. Microbiological Laboratory Diagnosis of Human Brucellosis: An Overview. *Pathogens*. 2021;10(12):1623. doi:10.3390/pathogens10121623
22. Wareth G, El-Diasty M, Abdel-Hamid NH, Holzer K, Hamdy ME, Moustafa S, et al. Molecular characterization and antimicrobial susceptibility testing of clinical and non-clinical Brucella melitensis and Brucella abortus isolates from Egypt. *One Health*. 2021;13:100255. doi:10.1016/j.onehlt.2021.100255
23. Díaz R, Casanova A, Ariza J, Moriyón I. The Rose Bengal Test in human brucellosis: a neglected test for the diagnosis of a neglected disease. *PLoS Negl Trop Dis*. 2011;5(4):e950. doi:10.1371/journal.pntd.0000950
24. Trotta A, Marinaro M, Cirilli M, Sposato A, Adone R, Beverelli M, et al. Brucella melitensis B115-based ELISA to unravel false positive serologic reactions in bovine brucellosis: a field study. *BMC Vet Res*. 2020;16(1):50. doi:10.1186/s12917-020-02278-7
25. Sadhu DB, Panchasara HH, Chauhan HC, Sutariya DR, Parmar VL, Prajapati HB. Seroprevalence and comparison of different serological tests for brucellosis detection in small ruminants. *Vet World*. 2015;8(5):561-6. doi:10.14202/vetworld.2015.561-566

26. Chisi SL, Marageni Y, Naidoo P, Zulu G, Akol GW, Van Heerden H. An evaluation of serological tests in the diagnosis of bovine brucellosis in naturally infected cattle in KwaZulu-Natal province in South Africa. *J S Afr Vet Assoc.* 2017;88(0):e1-e7. doi:10.4102/jsava.v88i0.1381
27. Akoko JM, Pelle R, Lukumbagire AS, Machuka EM, Nthiwa D, Mathew C, et al. Molecular epidemiology of *Brucella* species in mixed livestock-human ecosystems in Kenya. *Sci Rep.* 2021;11(1):8881. doi:10.1038/s41598-021-88327-z
28. Boukary AR, Saegerman C, Abatih E, Fretin D, Alambédji Bada R, De Deken R, et al. Seroprevalence and potential risk factors for *Brucella* spp. infection in traditional cattle, sheep and goats reared in urban, periurban and rural areas of Niger. *PLoS One.* 2013;8(12):e83175. doi:10.1371/journal.pone.0083175
29. Alavi SM, Alavi L. Treatment of brucellosis: a systematic review of studies in recent twenty years. *Caspian J Intern Med.* 2013;4(2):636-41.
30. Ranjbar M. Treatment of Brucellosis. In: Baddour, M. M., editor. *Updates on Brucellosis* [Internet]. London: IntechOpen; 2015 [cited 2022 Jun 23]. Available from: <https://www.intechopen.com/chapters/48725>. doi:10.5772/61093
31. Khan AU, Shell WS, Melzer F, Sayour AE, Ramadan ES, Elschner MC, et al. Identification, genotyping and antimicrobial susceptibility testing of *Brucella* spp. isolated from livestock in Egypt. *Microorganisms.* 2019;7(12):603. doi:10.3390/microorganisms7120603
32. Hosseini SM, Abbasalipourkabir R, Jalilian FA, Asl SS, Farmany A, Roshanaei G, et al. Doxycycline-encapsulated solid lipid nanoparticles as promising tool against *Brucella melitensis* enclosed in macrophage: a pharmacodynamics study on J774A.1 cell line. *Antimicrob Resist Infect Control.* 2019;8(1):1-2. doi:10.1186/s13756-019-0504-8
33. Ganesan P, Schmiedge J, Manchaiah V, Swapna S, Dhandayutham S, Kothandaraman PP. Ototoxicity: A Challenge in Diagnosis and Treatment. *J Audiol Otol.* 2018;22(2):59-68. doi:10.7874/jao.2017.00360
34. Esmailnejad-Ganji SM, Esmailnejad-Ganji SMR. Osteoarticular manifestations of human brucellosis: A review. *World J Orthop.* 2019;10(2):54-62. doi:10.5312/wjo.v10.i2.54
35. Hasanjani Roushan MR, Moulana Z, Mohseni Afshar Z, Ebrahimpour S. Risk Factors for Relapse of Human Brucellosis. *Glob J Health Sci.* 2015;8(7):77-82. doi:10.5539/gjhs.v8n7p77
36. Shevtsov A, Syzdykov M, Kuznetsov A, Shustov A, Shevtsova E, Berdimuratova K, et al. Antimicrobial susceptibility of *Brucella melitensis* in Kazakhstan. *Antimicrob Resist Infect Control.* 2017;6(1):1-5. doi:10.1186/s13756-017-0293-x
37. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol.* 2014;4:177. doi:10.3389/fphar.2013.00177
38. El-Dahiyat F, Rashrash M, Abuhamdah S, Abu Farha R, Babar ZU. Herbal medicines: a cross-sectional study to evaluate the prevalence and predictors of use among Jordanian adults. *J Pharm Policy Pract.* 2020;13(1):1-9. doi:10.1186/s40545-019-0200-3
39. Dadar M, Tiwari R, Sharun K, Dhama K. Importance of brucellosis control programs of livestock on the improvement of one health. *Vet Q.* 2021;41(1):137-51. doi:10.1080/01652176.2021.1894501
40. Yuan HT, Wang CL, Liu LN, Wang D, Li D, Li ZJ, et al. Epidemiologically characteristics of human brucellosis and antimicrobial susceptibility pattern of *Brucella melitensis* in Hinggan League of the Inner Mongolia Autonomous Region, China. *Infect Dis Poverty.* 2020;9(1):1-9. doi:10.1186/s40249-020-00697-0
41. Ghanbari MK, Gorji HA, Behzadifar M, Sane N, Mehedi N, Bragazzi NL. One health approach to tackle brucellosis: a systematic review. *Trop Med Health.* 2020;48(1):86. doi:10.1186/s41182-020-00272-1
42. Mathur S, Banai M, Cohen D. Natural *Brucella melitensis* Infection and Rev. 1 Vaccination Induce Specific *Brucella* O-Polysaccharide Antibodies Involved in Complement Mediated *Brucella* Cell Killing. *Vaccines (Basel).* 2022;10(2):317. doi:10.3390/vaccines10020317