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BURDEN OF HUMAN BRUCELLOSIS IN UGANDA: A REVIEW

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Abstract

Brucellosis is a zoonotic disease mainly acquired through consumption of infected animal products such as milk and meat. It is one of the leading zoonotic diseases and is a serious public health concern in endemic areas.Specifically, the review aimed at updating the burden of brucellosis in Uganda.Different research engines were utilised in writing this paper such as web of science, Pubmed Central, Scopus, Medline, Google Scholar, Researchgate, Academia Edu, etc.Prevalence of Brucellosis is low in Uganda. Being a Butcher, Milking, drinking raw milk are highly associated with brucellosis. The commonly used antimicrobials to manage Brucellosis are highly active against brucella except rifampicin. Brucella infection should be among the plan for treatment of febrile illness alongside malaria and Typhoid. Support is needed to allow more analysis on isolates such as sequencing and phylogeny analysis to learn more on the management of Brucella Epidemiology and ecology in this region.

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Introduction:-

Brucellosis is a zoonosis caused by Brucella species[1].With more than 500,000 new cases reported per year, brucellosis is still a major problem for people around the world [2-4]. Brucella suis, Brucella melitensis, and Brucella abortus, which also cause Brucellosis in goats, cattle, and pigs, respectively, are the major etiological agents of human brucellosis [5-7].Contact with sick animals or their fluids, inhalation of infectious aerosols, and consumption of infected animal products like meat and milk are all ways that the disease is passed from animals to humans [8]. It is a risk to those who work with animals, particularly veterinarians, scientists, lab technicians, abattoir employees, and farmers [9]. In humans, the most common symptoms of brucellosis are intermittent fever, fatigue, body aches, joint pains, back aches, chills anorexia, shivering and weakness. Complications like spondylitis, acute respiratory distress syndrome, meningitis, pericarditis, bronchopneumonia, unilateral epididymo-orchitis, wedge-shaped vertebral collapse and uveitis can be can occur [10].Effective human brucellosis prevention requires the

eradication of contaminated animals, immunization of healthy ones, avoiding intake of raw milk, and adequate heat treatment of raw milk [11].
The frequency of Brucellosis in sub-Saharan Africa is underreported and varies by nation, location, and animal variables [12]. Brucellosis is extensively documented in Uganda [11].

Most people in Uganda's cattle-keeping regions depend largely on animals for their livelihood [12]. In Uganda, it's thought that 92% of the raw milk is sold in unofficial marketplaces. As a result, many human brucellosis infections are anticipated [13]. Brucella seroprevalence in animals is typically strongly correlated with the presence of human brucellosis, as affected animals purposefully release the bacterium in milk, increasing the risk of infection in humans. [14].

Brucellosis

Brucellosis is a bacterial infection caused by a range of Brucella species which usually infect goats, cattle, sheep, pigs and dogs. Consuming tainted animal products and breathing infectious aerosol droplets are the two main ways the sickness is contracted. The majority of human cases of Brucella infection are caused by consuming unpasteurized milk or milk products from goats or sheep that have the disease [10]. Brucellosis is one of the leading zoonotic diseases and is a serious public health concern in endemic areas. The high rate of urbanization, increasing growth of animal industries and poor hygiene practices in animal husbandry during food handling is also responsible for persisting as a public health problem [10].

Brucella species are small, non-motile, non-sporing, non-capsulate, gram negative coccobacilli [15]. They grow aerobically however some strains need 5% carbondioxide for primary isolation. They grow slowly and therefore require at least 4 weeks incubation for primary isolation. Growth can be enhanced by enrichment with blood or serum. Brucella bacteria usually test positive for oxidase and catalase [15].

Genus Brucella is monospecific with varousbiovars. About 10 species make up the Brucella genus, including B. abortus, B. melitensis, B. suis, B. ovis, B. canis, and B. neotomae. B. pinnipedalis, B. microti, B. ceti, and B. inopinata. The four most common brucellosis-causing organisms in humans are B. abortus, B. suis, B. melitensis, and B. canis [16]. Despite the fact that any of these species can infect humans with brucellosis, Brucella melitensis is the most virulent and is the main cause of infections[17].

Pathogenesis of Brucellosis

Brucella bacteria enters the host usually through ingestion, inhalation and penetration of the conjunctiva or a wounded skin[18]. Upon invasion, Brucella organisms are taken up by neutrophils, dendritic cells, and macrophages and transported to lymph nodes [19]. Clinical features of human brucellosis such as osteoarticular manifestations, hepatosplenomegally and lymphadenopathy occur following invasion of the reticuloendotherial system [10]. In both phagocytic and non-phagocytic cells, Brucella bacteria can enter, persist, and reproduce. This is what gives the bacteria its virulence. Pathogenic characteristics of Brucella such as GMP and AMP production as well as outer membrane proteins inhibits activation of bactericidal substances, phagolysosome fusion and production of TNF. Analysis of gene sequences of Brucella species have revealed absence of key virulent factors such as exotoxin, endotoxin, capsule and fimbriae[19]. The intracellular localization of Brucella bacteria is responsible for its ability to evade host immune responses but also protects it from antimicrobials [20].

Macrophages, trophoblast cells and dendritic cells are the main target cells for this bacterium. However, Brucella bacteriamay also replicate within other cells, such as murine fibroblasts or epithelioidcells [21].By sidestepping the host's immunological response in macrophages, Brucella is able to survive, replicate, and spread to other tissues via cellular tropism. Brucella species use a zipper-like method to enter the host cells [22].The occurrence of Brucella infection depends onthe virulence of the Brucella species, exposuredose,andnatural resistance of the host to the organisms[23].

The target tissues in the reproductive organs are where the pathogen first spreads throughout the host through the lymph glands [19]. In the end, Brucella promotes acute or persistent infection of the reproductive system, which causes serious illnesses of the reproductive tract or abortion [24].

Clinical presentation

Brucellosis is a febrile illness that presents with a wide range of clinical spectrum [25]. The incubation period ranges from 7-28days.The disease develops gradually with malaise, fever, general body weakness, joint aches, muscle aches and sweating. The fever usually increases in the afternoon and reduces during the night together with drenching sweat. Gastrointestinal and nervous manifestation may occur. Hepatitis may be accompanied by enlargement of lymph node. Splenomegaly accompanied by hepatitis also occur [26].

There may be osteomyelitis which present in form of deep pain and motion disturbances especially in vertebral bones. Features of generalized Brucella infection usually resolve in weeks or months though focal lesions and symptoms may persist. A chronic illness may develop following initial infection and is characterized by malaise, joint pains, body aches, nervousness and other non-specific symptoms similar to psychoneurotic manifestations [26].

The isolation of the organism, the detection of antibodies specific to Brucella, and the detection of genetic material from the Brucella organism are all methods of laboratory examination that can be used to confirm the diagnosis of Brucellosis [27].

Although considered the best method, Blood cultures for Brucella isolation have low sensitivity. Brucella can be quickly detected and confirmed using polymerase chain reaction, but these methods currently lack the necessary infrastructure, tools, and experience. Among other immunological tests, Brucellosis has been diagnosed using the enzyme-linked immunosorbent assay, florescence polarization assay, and Rose Bengal plate agglutination assay [28].

Isolation and identification of Brucella species

Culture is referred to as the gold standard for the laboratory diagnosis of Brucellosis. Blood cultures should always be done immediately Brucellosis is suspected because Brucellosis has an initial bacteremic phase in its pathogenesis. it is considered an important method for confirming the infection however presents with poor sensitivity ranging from 10% to 90% [15].

Blood clot cultures (blood clots in which leukocytes carrying phagocytosed organisms are cultured), lysis-based blood cultures (white blood cells are broken by saponin to release Brucella prior to inoculating them onto culture media), lysis-based blood cultures using manual monophasic and biphasic methods, and automated new generation BC systems, the most popular of which are the Bacterc 9000 or bactec FX series from Becton Dickin Utilizing sophisticated blood culture equipment increases the sensitivity of blood cultures and speeds up the detection of Brucella [29].

Identification of suspected colonies must be performed using biochemical as well as serological tests. Brucella species has been cultured mainly on blood agar and chocolate agar and incubated for 24-72hrs. Colonies are small (2mm), convex, non-pigmented, non-hemolytic with centre edge and frequently smooth however Brucella can produce rough variants [30]. The gram staining reaction of the organism, which is a gram negative very small coccobacilli with a fine sand look that typically forms clusters termed microcolonies, can be used to assume the identity of Brucella [31]. Conventional phenotypic methods such as catalase, oxidase, urease, production of Hydrogen peroxide, fermentation of sugars and sensitivity to dyes such as basic fuchsin, carbondioxide requirement and motility tests have been used [32].

In addition to phenotypic tests, matrix –assisted laser desorption ionisation time of flight analysers can be employed to identify Brucella bacteria to specie level however its accuracy is sometimes controversial [32].

Prevalence of Brucellosis in Africa

Prevalence of human Brucellosis is underreported in sub-Saharan Africa and differs from county to county, geographical areas as well as animal factors [12]. In South Sudan, prevalence was reported to be at 32.1% in slaughter house workers. In Libya, seroprevalence of over 40 % has been documented [33].

Among abattoir employees in Nigeria, the seroprevalence of brucellosis was high (33.5%). The linked risk variables were helping with animal parturition, working in the abattoir while having an open cut or wound, and eating while working in the abattoir [34].

Using the Complement Fixation Test and the Rose Bengal Test, it was discovered that Ethiopia had a 4.7 and 1.3% prevalence of brucellosis, respectively. This was related to the fact that a large percentage of abattoir workers consumed raw meat and dairy products while killing and eviscerating animals without wearing protective equipment [35].
The prevalence of brucellosis among abattoir workers in Cameroon was reported to be 5.6%. This was correlated with the following factors: failure to wear protective equipment at work, consumption of raw milk, handling of fetuses, occupational exposure lasting more than five years, knowledge of brucellosis, and ownership of and contact with livestock outside of the abattoir and home environments [36].

A 20.3% estimated total seroprevalence of Brucella was found in Zambia. Breeding practices and abattoir workers who had blood splashed in their mouth while doing their duties were linked to this [37].

The prevalence of Brucellosis was high (48.4%) overall in Mwanza, Tanzania. Compared to meat dealers (14%), abartoirs workers had a larger prevalence (39%) than them. This may be because they had more direct contact with animals, especially their fetuses, during the killing process, making them more susceptible to infection than meat sellers. Long work hours also played a role in the high Brucella seopositivity. This may be explained by the fact that those who worked longer shifts in the abattoir had a higher chance of exposure than those who worked shorter shifts. Compared to Brucella abortus (46.0%), the seroprevalence of Brucella melitensis (23.6%) was much lower. This disparity between sheep and goats, who are more likely to be infected with B. melitensis, and cattle, which is the principal host of B. abortus and the most murdered animals in the city abattoir, could perhaps be explained [38].

In a pastoralist community in Kenya, there were 84 cases of human brucellosis per 100,000 people each year (Munyua et al., 2021). The incidence in this pastoral area was 2.5 times higher than the Kilimanjaro region's documented rates of 33 per 100,000 people in 2008 and 35 per 100,000 people in 2014 [39].

Burden of Human brucellosis in Uganda

Human brucellosis is largely distributed in many parts of Uganda [11]. Brucellosis seroprevalence was at 10% among abattoir workers in main abattoirs in Kampala and Mbarara. 9% of them had full protective gear and could have acquired the disease through inhalation of infectious aerosols. 23% of them had no protective gear and could have acquired the infection via physical contact with infected animals or their fluids [40]. In northern Uganda, brucellosis prevalence was found to be 18.7% among feverish patients. Consuming raw milk or milk products and maintaining cattle or other livestock were factors that were strongly associated with the infection [41].

The seroprevalence of brucellosis in agropastoral settlements in the Kiboga district was determined to be 17%. Living alone, in a rural environment, and consuming locally produced milk products were the risk factors linked to human brucellosis [42].

12 % prevalence of Brucellosis was recorded among butchers in Kampala districts and this was attributed to mainly lack of protective gear during slaughter[41]. In the Wakiso district, feverish outpatients who tested negative for malaria had a 7.5% sero-positivity rate for Brucella abortus. Having a Muslim background and consuming unpasteurized milk were risk factors for B. abortus [43].

The seropositivity of brucellosis in household members engaged in cattle keeping in south western Uganda was high at 13.4% [44]. Brucellosis prevalence in South-western Uganda was found at 14.9%. Consumption of raw milk, family of brucellosis and contact of hides and skin were significantly associated with the high prevalence [45]. 14.4% of people in pastoralist villages in south-western Uganda had brucellosis, according to ten-year retrospective research[46].

The seroprevalence of Brucellosis in smallholder households in the Iganga district was found to be 4.4%, and the consumption of dairy products produced locally was linked to the seropositivity [47].

In Mbarara district, Brucellosis sero-prevalence among exposed livestock caretakers was reported to be 5.8%, and drinking unpasteurized milk was substantially linked to the seropositivity [11].

Antimicrobial susceptibility testing

Methods for antimicrobial susceptibility testing, such as disc diffusion, broth dilution, and agar dilution procedure, have been demonstrated to consistently produce correct results [48].

Disc diffusion method

A known concentration of an antimicrobial agent is diffused into solid culture media that has been infected with a known test organism growing in pure culture using the antimicrobial sensitivity testing technique known as disc diffusion. The disc diffusion method's foundation is the identification of an inhibition zone that is inversely proportionate to the bacterial susceptibility to the antibiotic. When the antimicrobial agent diffuses into the seeded culture media, a gradient of the antibiotic develops. The zone of inhibition is created when the antimicrobial agent's concentration falls to the point where it can no longer stop the development of the test organism [48].

The minimum inhibitory concentration for that specific bacterium/antimicrobial combination is correlated with the diameter of this zone of inhibition encircling that antimicrobial disc. The test bacterium's MIC is inversely correlated with the zone of inhibition. Generally speaking, the bigger the zone of inhibition, the less antibiotic is needed to stop the growth of the organisms. However, this depends on the antimicrobial's concentration and diffusibility in the disk [48].

Zones of inhibition can take some effort to determine manually. Automated zone reading devices integrated with legislative reporting and data handling systems can be used to remedy this.The disks should be equally distributed on the culture media to prevent the disc diffusion test's zone of incubation from crossing over into the zone of inhibition around the antimicrobial disks. Inhibition zones are prevented from overlapping by keeping discs 24 mm apart, but this depends on how well the antimicrobial diffuses in the agar and how concentrated the discs are [48].

Broth and agar dilution methods

The goal of the broth and agar dilution procedures is to identify the minimal antimicrobial agent concentration that prevents the tested bacterium from growing visibly. However, the MIC typically does not offer absolute values. The real MIC is found between the test concentration that stops bacterial growth at the lowest level and the test concentration below that level. As a result, it is possible to assume that MIC measurements utilizing a series of dilutions yield an inherent variation of one dilution. The right antimicrobial susceptibility dilution procedures have demonstrated to be more consistent and quantitative than agar disc diffusion, and antimicrobial reference ranges should take into account interpretation criteria (sensitive, intermediate, and resistant) for a certain bacterium/antimicrobial combination. Antibiotics are typically measured in doubling dilutions, though, which can result in inaccurate results [48].

Broth dilution method

A suspension of bacteria at a specific and appropriate concentration is tested in a liquid medium with known documented formulations against various concentrations of an antibacterial agent (often serial two-fold dilutions). Either the macrodilution method, which uses minimum volumes of 2 ml in tubes, or the microtitre plate method, which uses smaller volumes, can be utilized for the broth dilution procedure. Commercially available microtitre plates with lyophilized, predilited antibacterials in the wells are widely available. To minimize discrepancies that can occur as a result of the manufacture and dilution of antimicrobials from various laboratories, identical batches have been used in microdilution plates. The use of microtire plates with a specified test technique that also defines suitable reference species makes it easier to compare lab results [48].

Because they are generated commercially, the majority of broth microdilution antimicrobial tests are more adaptable to changing monitoring program requirements than agar dilution or disk diffusion. Because antimicrobial plates and related equipment might be expensive, some laboratories might not be able to use this procedure [48].

Agar dilution method

Agar dilution is a technique in which various antimicrobial agent concentrations are added to agar medium, often using serial two-fold dilutions, then a predefined bacterial inoculum is applied to the agar surface of the plate. This method has proven to yield the most accurate findings for MIC test organism/antimicrobial combination determinations [48].

Antimicrobials used in management of Brucellosis

Brucellosis is managed using antibiotics however the most effective antibiotic combination and durations of treatment are not clear [49]. Most experts recommend regimens with two or more antibiotics because of a high relapse rate associated with monotherapy [15]. WHO suggested an antibiotic combination in 1986 for the treatment of brucellosis, consisting of oral doxycycline 100 mg twice daily for 6 weeks and oral rifampicin 600 to 900 mg daily for 6 weeks, or streptomycin 1g intramuscularly daily for 2-3 weeks.

This treatment remains accepted as the preferred treatment by most infectious diseases experts [50]. Due to its simplicity of administration and cheaper cost, the rifampicin plus doxycycline regimen is the most frequently prescribed treatment and preferable to the more successful streptomycin regimen [15]. Streptomycin needs parenteral administration in hospital or any health care setting, both of which are limited in developing countries [15].

The treatment regimens mentioned above were again included in 2006 WHO guidelines [10] Guidelines developed at a global conference of experts in Loanina, Greece, identified the streptomycin plus doxycycline regimen as the gold standard for treating brucellosis [51]. Other antimicrobial combinations such as quinolones (eg ofloxacin and ciprofloxacin) and cotrimoxazole have been used although their effectiveness is still questionable [10]. Additionally, some researchers have found that tetracycline therapy is less expensive and simpler to give than combination medications, but there is insufficient and conflicting evidence to support this claim [52].

Antibiotic susceptibility patterns of Brucella species

Doxycycline, Tetracyclines, Gentamicin, Ciprofloxacin, Levofloxacin, Chloramphenicol, Streptomycin, Trimethoprim/sulfamethoxazole, and Tigecycline were found to be effective against Brucella strains. Resistance to Azithromycin and Rifampicin was detected in a study conducted in Egypt between 2018 and 2020 [53].

Tetracycline, streptomycin, Ciprofloxacin, Trimethoprim-suphamethoxazole, and other antibiotics were effective against all Brucella isolates. Probable resistance to Cenfapicin and Rifampicin was observed in 277(64) and 7(2%) isolates respectively according to a study conducted in Egypt between 1999 and 2004 [54].

A study conducted in Malaysia from 2010 to 2011 found that all isolates were sensitive to every antimicrobial drug tested, with the exception of rifampicin, for which 30 out of 41 isolates tested had increased MIC > 1 μg/mL [55].

According to a 2014 study done in Markazi Province, 100% of the Brucella isolates was susceptible to Tetracycline, Minocycline, Gentamicin, and Tigecyclin; 93.3% was susceptible to Doxycycline; 66.7% to Co-amoxiclave; 44.7% to Rifampin; 86.7% to Streptomycin; 80% to Ciprofloxacin; 76.7% to Cotrimoxazole and 73.3% to Ceftriaxone [56].

A study conducted in Eastern Turkey between 2004 and 2018 found that, based on minimum inhibitory concentrations (MIC) 90 values, Ciprofloxacin was the most active agent, followed by Doxycycline and Streptomycin, in that order. Although all isolates were sensitive to Doxycycline, Streptomycin, and Ciprofloxacin, 18(20.7%) strains were found to be moderately susceptible to Rifampicin, with the highest values of MIC50 and MIC90 [57].

A study conducted in Iran from 2016 to 2018 found that most tested antibacterial drugs, with the exception of Ampicillin-sulbactam, were effective against isolates of Brucella melitensis in the disk diffusion method and E-test (MIC). Rifampicin and Ampicillin-sulbactam probable resistance was found in 60(100%), 1(1.7%), 11(18.4%), and 2(3.4%) isolates, respectively [58].

According to a study done in Eastern Anatolia Turkey 2012, the resistance to Streptomycin, Ciprofloxacin and Gentamycin was determined at the rate of 7.3% and to Rifampicin at the rate of 9.7%. The highest (46.3%) resistance was determined against Trimethoprim-sulfamethoxazole. All strains were found to be sensitive to Tetracycline at the rate of 100.0% [59].

Doxycycline, Streptomycin, Gentamycin, Trimethoprim-sulfamethoxazole, Ciprofloxacin, Ampicillin, and Amoxicillin/clavulonic were all effective against all isolates of Brucella. All of the strains produced intermediate sensitivity (22%) to Rifampicin and one strain was resistant (2%) while the others were all sensitive according to a study conducted in Adana, Turkey between 2010 and 2012 [60].

According to a study conducted in Northeast China, all of the Brucella isolates (100%) were sensitive to levofloxacin, ciprofloxacin, doxycycline, tetracycline, minocycline, gentamicin, and streptomycin. However, 24.6%, 86.9%, 65.6%, 27.9%, 3.3% and 1.6% of the isolates were resistant to Rifampin, Azithromycin, Cefepime, Cefoperazone/sulbactam, Cefotaxime, and Meperidine/sulfamethoxazole respectively [60].

Comorbidities of Brucellosis

A study ccarried out at Kabala Regional Referral Hospital indicated that some of the Brucellosis cases were co-infected with Human immunodeficiency virus(16%), multiple cormobidities (14%), Syphilis (12%), tuberculosis (3%) and other comorbidities in smaller numbers [62]. A study carried out in Northern Tanzania among hospitalised febrile patients indicated many comorbidities were detected in some Brucellosis cases including HIV, Plasmodium falciparum, Salmonella typhi, Leptospirosis, Spotted fever group Ricketsiosis, Typhus and acute Q fever [63].

Conclusion:-

Prevalence of Brucellosis was low. Being a Butcher, Milking, keeping animals at home and drinking raw milk were associated with Brucellosis. The commonly used antimicrobials to manage Brucellosis are highly active against Brucella bacteria except Rifampicin which should be used with caution and under unavoidable circumstances. Brucellosis can exist in isolation or with any comorbidity however it is not associated with any comorbidity.

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