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Review on Bovine Tuberculosis and its Public Health Importance

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Abstract: Bovine tuberculosis is a chronic and contagious disease of cattle and other domestic and wild animals including human. *Mycobacterium bovis* (*M. bovis*) is a causative agent which is a member of the Mycobacterium tuberculosis complex, a group of mycobacterial species that includes *M. tuberculosis, M. bovis*, *M. africanum* and *M. microti.* Tubercle bacilli gain entrance to the animal body through respiratory, alimentary, genital, cutaneous and genital routes. The first two are being the most commonly observed routes of infection resulting in pulmonary and extra-pulmonary form of the disease, respectively. Early infections are often asymptomatic. In the late stages, common symptoms include progressive emaciation, a low-grade fluctuating fever, weakness and inappetence. Animals with pulmonary involvement usually have a moist cough that is worse in the morning. The diagnosis of BTB can be made by direct and indirect methods, in which we can mention clinical, *post mortem*, histopathological, immunological, bacteriological and molecular methods. The main reservoir of *M. bovis* is cattle. The probability of infection with *M. bovis* is influenced by factors, which are linked to environment, host and the pathogen itself., Human infection due to the inhalation of infected droplets released by animals. Bovine tuberculosis can be controlled by test-and-slaughter or test and segregation methods.

Key words: Bovine・Diagnosis・Mycobacterium Bovis・Tuberculosis・Zoonotic

INTRODUCTION

Globally the growing demand of livestock products, milk and meat, livestock revolution and livestock production is changing from a substance activity to global food activity. On the other hand population of Ethiopia has increased dramatically in the last two decades from approximately 55 million people in 199 to current estimate of around 85 million [1]. Increased population size lead to an inexorable increase in demand for food, putting pressure on the agricultural sector in which 85% of the work force is employed. Ethiopia has the largest livestock population in Africa, including an estimated, 53.99 million cattle that contribute to the livelihoods of 60-70% of the population Central Statistical Agency [2]. The vast majority of the cattle are indigenous zebu (Bos indicus) managed hander traditional husbandry system (grazing in the field) in rural areas, However in recent years the number of dairy cattle of highly productive exotic (Bos Taurus, mainly Hosten-Friesian) and cross breeds has been on the rise, particularly in urban and pre-urban areas in response to the increasing demand for milk products and the Ethiopian government's effort to improve productivity in the livestock sector. Bovine tuberculosis is a chronic and contagious disease of cattle and other domestic and wild animals including human [3].

Mycobacterium bovis (M. bovis) is a causative agent which is a member of the Mycobacterium tuberculosis complex, a group of mycobacterial species that includes M. tuberculosis, M. bovis, M. africanum and M. microti. From those, M. bovis is the most universal pathogen for the disease bovine tuberculosis among mycobacterium in species and affects many vertebrate animals of all age groups including human although, cattle, Goats and Pigs are found to be most susceptible, while sheep and horses are showing a high natural resistance and the disease is characterized by progressive development of tubercles in any tissue /organ of the body [4]. Characteristic tuberculosis lesion occur most frequently in the lung and retropharyngeal, bronchial and mediastinal lymph nodes. Lesions can also be found in the mesenteric

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lymph nodes, livers, spleens, on serous membranes and in other organs [5]. Prevalence data on BTB infection in Africa is scarce. There is, however, sufficient evidence to indicate that it is widely distributed in almost all African countries and even is found at high prevalence in some animal populations [6]. However, in the tropical countries including Ethiopia, BTB has been found to affect a higher proportion of exotic breeds than local zebus, which has been conferred through prevalence studies of BTB in different parts of Ethiopia [7]. The economic impact of BTB has also been reported [8]. Its zoonotic implication has also significantly indicated an increasing trend to be of public health hazards [9]. Bovine tuberculosis diseased animal loses 10 to25% of their productive efficiency, direct lose due to the infection become evident by decrease in 10 to 18% milk and 15% reduction meat production [10].

Apart from effects on animal production, it has also a significant public health importance [11]. Currently, the disease in human is becoming increasingly important in developing countries, as humans and animals are sharing the same micro environment and dwelling premises, especially in rural areas and susceptibility of AIDS patients to tuberculosis [8]. It is estimated that M. bovis cause 10 to 15% human case of tuberculosis in countries where pasteurization of milk is rare and bovine tuberculosis is common [12]. Therefore the objective of this seminar paper is to review available literatures on bovine tuberculosis and its zoonotic implication.

Literature Review

Etiology: *Mycobacterium* belongs to the Kingdom of Bacteria; Phylum of Actinobacteria; Order of Actinomycetes; Family of *Mycobacteria*ceae. They are grouped in the suprageneric rank of actinomycetes that, usually, have a high content (61-71%) of guanine plus cytosine (G+C) in the genomic deoxyribonucleic acid (DNA) and a high lipid content in the wall, probably the highest among all bacteria [13]. Bovine tuberculosis is a chronic infectious disease caused by both *M. bovis* and *M. caprae* which belong to the *Mycobacterium tuberculosis* complex (MTC) group *M. bovis* and *M. caprae* can also affect other domestic and wild animals as well as humans [14].

Other members of the MTC group such as *M. tuberculosis, M. africanum* and *M. Canetti* are predominantly human pathogens. although infections with *M. tuberculosis* in cattle have been reported MTC group members are commonly considered as subspecies and are 99.9% similar at the nucleotide level, but differ widely in terms of their host tropisms, phenotypes and pathogenicity. The thick and lipid- rich cell wall of mycobacteria protects DNA from attack of lytic enzymes after autolysis and necrosis of the host cell. *Mycobacteria* are thin rods of varying length (0.2-0.6 by 1.0-10.0µm) and sometimes branching filamentous, non-motile, non-spore forming, aerobic and oxidative. *M. tuberculosis* is straight or slightly curved rod, whereas *M. bovis* is usually straighter, stouter and shorter [15]. All *Mycobacteria* are acid fast and share a characteristics cell wall, thicker than many other bacteria, which is hydrophobic, waxy and rich in mycolic acid/mycolates [13].

Pathogenesis: Tubercle bacilli gain entrance to the animal body through respiratory, alimentary, genital, cutaneous and genital routes. The first two are being the most commonly observed routes of infection resulting in pulmonary and extra-pulmonary form of the disease respectively. After infection the bacteria may localize in tissue related to the route of infection and associated lymph nodes [16]. *Mycobacterial* infection triggers a Th1-induced cell mediated immune response (CMI) which leads to release of cytokines of such as tumor necrosis factor-α, Interleukin-12 (IL-12) and interferon gamma (IFN-γ). This pathway is essential to activate macrophages [17]. Depending on the balance of cytokines involved, three outcomes are possible: 1) macrophages kill and eliminate the bacteria, 2) the bacteria lies dormant (latency), 3) the bacteria cannot be contained by the immune system and the disease develops to active TB [18].Containment of the bacteria results in the formation of nonvascular nodular granulomas known as "tubercles". Lesions show typically a center of caseous with some degree of calcification surrounded by a cell wall of epithelioid cells, lymphocytes and neutrophils [19].

The initial CMI response is followed later in time by a humoral antibody response, which is caused by a shift of Th1 to Th2 cell activation [20]. CMI response can be affected by the animal's nutritional state (e.g. deficiency in energy, protein and micro nutrients), by stress or concurrent diseases, which lead to a reduction of the host resistance [21]. The *Mycobacteria* are intra-cellular organism in which the ability to produce diseases in animals depends on their virulence factor, appear to be related to the ability to survive and multiply within microphages [13].

Virulence appears to reside in the lipids of the wall. Mycosides, phospholipids and sulpholipids are thought to protect the tubercle bacilli against phagocytosis. Glycolipids cause granulomatous response and enhance the survival of phagocytized *Mycobacteria*. Wax D and various tuberculo protiens induce a delayed hypersensitivity reaction detected in the tuberculin test [22].

Clinical and Pathological Findings: Early infections are often asymptomatic. In the late stages, common symptoms include progressive emaciation, a low-grade fluctuating fever, weakness and in appetence. Animals with pulmonary involvement usually have a moist cough that is worse in the morning, during cold weather or exercise and may have dyspnea or tachypnea. In the terminal stages, animals may become extremely emaciated and develop acute respiratory distress. In some animals, the retropharyngeal or other lymph nodes enlarge and may rupture and drain [23].

Greatly enlarged lymph nodes can also obstruct blood vessels, airways, or the digestive tract. If the digestive tract is involved, intermittent diarrhea and constipation may be seen. During post mortem examination bovine tuberculosis is characterized by the formation of granulomas (tubercles) where bacteria have localized. These granulomas are usually yellowish and caseous, ceso-calcareous or calcified, they are often encapsulated. Meat inspection officers are trained to check for military tubercles in the head, spleen, kidney, mammary glands, fore and hind- limbs, lungs, livers, heart and associated lymph nodes [24].

Epidemiology

Source of Infection and Mode of Transmission: The main reservoir of *M. bovis* is cattle, which can transmit the infection to many mammalian species including man [25]. Organisms leave the host in respiratory discharges, faeces, milk, urine, semen and genital discharges. These body excretions may contaminate grazing pasture, drinking water, feed, water and feed troughs or fomites, which may act as source of infection to other animals [26]. Inhalation of *M. bovis* bacilli is the most common route of infection with only a small number of mycobacteria required tocause an in fection and spread of the infection can happen between animals when that are confined together in the same air space, such as during housing over the winter period [27]. A secondary source of infection is the ingestion of contaminated milk or contaminated pasture and water

Risk Factors: The probability of infection with *M.bovis* is influenced by factors, which are linked to environment, host and the pathogen itself [9].

Environment: Housing predisposes to the disease, as do high stocking intensity and a large number of animals on a farm so that the disease is more common and serious where these forms of husbandry are practiced. The closer the animals are in contact the greater is the chance that the disease will be transmitted [28].

Agent: The causative organism is moderately resistant to heat, desiccation and many disinfectants. It is readily destroyed by direct sunlight unless it is in a moist environment. In warm, moist, protected positions, it may remain viable for weeks [29].

Host Range: Cattle are the primary hosts for M. bovis, but other domesticated and wild mammals can also be infected. Known maintenance hosts include brush tailed opossums (and possibly ferrets), badgers, bison and elk and kudu and African buffalo [9]. Species reported to be spillover hosts include sheep, goats, horses, pigs, dogs, cats, ferrets, camels, llamas, many species of wild ruminants, large cats (including lions, tigers, leopards, cheetahs and lynx) and several species of rodents. Some avian species, including mallard ducks, appear to be resistant to experimental infection. Zebu (Bos indicus) type cattle are thought to be much more resistant to tuberculosis than European cattle [9].

Distribution: Although bovine tuberculosis was once found worldwide, control programs have eliminated or nearly eliminated this disease from domesticated animals in many countries [30]. Nations currently classified as tuberculosis free include Australia, Iceland, Denmark, Sweden, Norway, Finland, Austria, Switzerland, Luxembourg, Latvia, Slovakia, Lithuania, Estonia, the Czech Republic, Canada, Singapore, Jamaica, Barbados and Israel [31]. Eradication programs are in progress in other European countries, Japan, New Zealand, the United States, Mexico and some countries of Central and South America. Bovine tuberculosis is still widespread in Africa, parts of Asia and some Middle Eastern countries [32].

Diagnosis

Clinical Diagnosis: Tuberculosis (TB) is usually a chronic debilitating disease in cattle, but it can occasionally be acute and rapidly progressive. In countries with eradication programs, most infected cattle are identified early and symptomatic infections are uncommon. In the late stages, common symptoms include progressive emaciation, a low-grade fluctuating fever, weakness and in appetence. Animals with pulmonary involvement usually have a moist cough that is worse in the morning, during cold weather or exercise and may have dyspnea or tachypnea [33].

Post Mortem Diagnosis: This disease is characterized by the formation of granulomas where bacteria are located. These granulomas are usually yellowish and either caseous, caseo-calcareous or calcified and often encapsulated. In cattle, tubercles are found in the lymph nodes, particularly those of the head and thorax. They are also common in the lung, spleen, liver and the surfaces of body cavities [34].

Histopathological Diagnosis: A presumptive diagnosis can also be made by histopathology and/or the microscopic demonstration of acid-fast bacilli, as a complementary form of *post mortem* lesions diagnostic presumptive BTB. More direct methods for tuberculosis diagnosis are based on the isolation or detection of the bacterium in sputum samples or biopsies (mostly in humans) or at *post mortem*, from tuberculous organ lesions (generally in animals). The presence of mycobacteria in a given sample can be assessed by Ziehl-Neelsen staining followed by light microscopy or aura mine O staining and fluorescence microscopy. These techniques are based on the tinctorial properties common in mycobacteria and microorganisms of the genus *Nocardia, Rhodococcus* and *Corynebacterium,* known as acid resistant bacilli. That is named because they can retain the fuchsine-heated material after treatment for alcohol-acid. In this type of coloring, alcohol acid resistant microorganisms can be observed under the microscope [35].

The presumptive diagnosis of mycobacteriosis can be made if the tissue has characteristic histological lesions such as caseous necrosis, mineralization, epithelioid cells, multinucleated giant cells and macrophages. As lesions are often paucibacillary, the presence of acid-fast organisms in histological sections may not be detected, although *M. bovis* can be isolated in culture. However, large numbers of acid-fast organisms are seen in lesions in primates, felids, mustelids (badgers) and marsupials [36].

Immunological Diagnosis: The immunological diagnosis of BTB is based on delayed-type hypersensitivity (DTH) reaction *in vivo*, represented by the tuberculin skin test (TST) [37]. This evidence is an indirect method of diagnosis of TB and can reveal incipient infections, with three to eight weeks after contact with the *M. bovis,* since techniques are employed using standard reagents and equipment. It is a test widely used since it was recommended by Robert Koch in 1890 [38]. The tuberculin by Koch's discovery, after some modifications, is currently called purified protein derivative (PPD), widely used for the indirect diagnosis of BTB *in vivo.* Advantages for the use of PPD and reasons for its wide use is low costs, high availability, long history of use and, for a long time [37].

Gamma Interferon Assays: Since 2006, the IFNγ assay (Bovigam®, Prionics, Switzerland) is an assay through which it is possible to verify the existence of cell-mediated immune response developed by the body of the animal in response to mycobacterial infection. IFNγ produced by T lymphocytes of the infected animal is detected, using monoclonal anti-IFNγ. The lack of detection of IFNγ characterizes the negativity of the animal to infection *M. bovis* since lymphocytes from uninfected cattle do not produce this cytokine in specific ways. The detection of bovine IFN-γ is carried out with a sandwich ELISA that uses two monoclonal antibodies to bovine gamma-interferon. It is recommended that the blood samples be transported to the laboratory and the assay set up as soon as practical, but not later than the day after blood collection [38].

Enzyme-linked Immunosorbent Assays (ELISA): The indirect ELISA technique measures the binding of specific antibodies to an antigen [39]. An advantage of the ELISA is its simplicity, but sensitivity is limited mostly because of the late and irregular development of Humoral immune response in cattle during the course of the disease. In order to diagnose cattle infected by *M. bovis*, antigens usually employed are the PPD and single or associated purified antigens from *M. bovis* such as antigens of the Ag85 that complex represents a major part of the secreted proteins and MPB70 and it highly homologous protein MPB83, secreted mycobacterial proteins with limited species distribution. Most of these antigens have achieved a sensitivity and specificity of around 90% and their recommendations are based on the existence of anergic animals, as well as increased antibody titers in more advanced stages of the disease [40].

Bacterial Isolation: Isolation of *M. bovis* is considered "gold standard" for BTB diagnosis. However, the long period required for the isolation and biochemical identification, is one of its critical points and may require more than twelve weeks to complete the final diagnosis

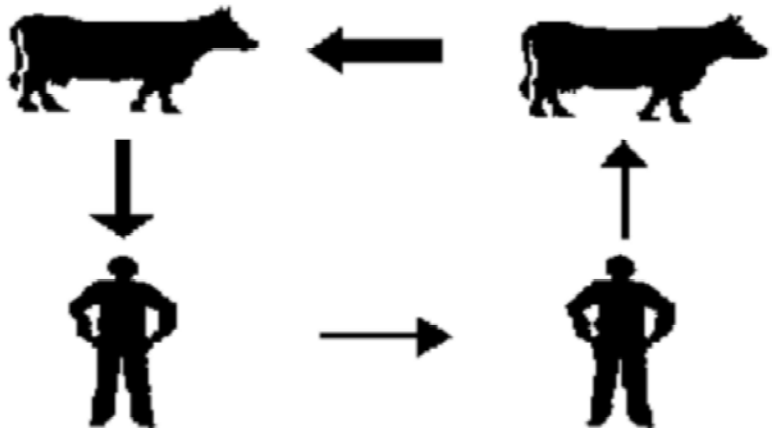

Fig. 1: Cycle of *M.bovis* transmission between cattle and humans the thickness of arrows suggests level of probability. Source: [45].

and also low sensitivity [41]. The samples collected are submitted to decontamination methods, involves the addition of NaOH, H_2SO_4, oxalic acid, or quaternary ammonium compounds, to eliminate such competitive microorganisms and, unfortunately, the toxic effects may affect mycobacterial viability, thereby interfering with culturing the organism [42].

Molecular Diagnosis: Polymerase chain reaction (PCR) has been successfully applied to detect members of the *M. tuberculosis* complex and is especially useful for the direct detection of *M. bovis* in bovine tissue samples [43]. The addition of assays such as PCR for detection of *M. bovis* DNA from formalin-fixed specimens has further enhanced some surveillance. PCR assays to detect MTB bacteria are currently less sensitive than culture techniques. The availability of the genome sequence of *M. tuberculosis* allows us to perform comparative analyses that are providing insight into some of the key differences between the human and bovine bacillus [44]. *M. bovis* is a close relative of *M. tuberculosis* and they share genetic identity over 99% at the whole genome level and identical 16S rRNA sequences [39].

Public Health Significance of Bovine TB: Zoonotic TB is mainly caused by *Mycobacterium bovis* and *Mycobacterium caprae* It is associated mainly with the ingestion or handling of contaminated milk and dairy products. Human infection due to the inhalation of infected droplets released by animals or because of contact with infected droplets in mucous membranes and broken skin is associated to groups of people that are in close contact with animals, such as slaughterhouse workers, farmers, etc. [33]. In developing countries, zoonotic TB constitute a major public health concern and it is therefore considered as a "neglected zoonotic diseases". The disease is mainly contracted by the consumption of raw milk and dairy products. Besides, in some areas of Africa there is a tradition of sharing shelter with animals and to consume raw milk, which may also contribute to disease dissemination [12].

Treatment, Control and Prevention: Because of economic and the public health hazards inherent in the retention of the tuberculous animals, antituberculous chemotherapy of animals is discouraged. In countries with eradication programmes treatment is generally discouraged or illegal [3]. The course of treatment for humans with bovine TB takes 6 to 9 months and the success rate following treatment is more than 95 percent [46]. Bovine tuberculosis can be controlled by test-and-slaughter or test-and-segregation methods. Affected herds are re-tested periodically to eliminate cattle that may shed the organism; the tuberculin test is generally used. Infected herds are usually quarantined and animals that have been in contact with reactors are traced. Only test-and-slaughter techniques are guaranteed to eradicate tuberculosis from domesticated animals. Effective disinfectants include 5% phenol, iodine solutions with a high concentration of available iodine, glutaraldehyde and formaldehyde. *M. bovis* is also susceptible to moist heat of 121°C for a minimum of 15 minutes [22].

Bovine TB has been reduced from domestic cattle in many developed countries by the application of a test-and-cull policy that moves. Therefore, creating awareness among the people, to meet the standard hygienic requirement and to improve husbandry practices is of paramount importance. In intensive dairy farms, building of the new premises needs to be done according to designs appropriate to dairy farms taking into account space per-cow, proper manure disposal and good ventilation and lighting systems. Pasteurization of milk and milk products should be done as routine practice most notably in rural communities.

CONCLUSION AND RECOMMENDATIONS

Tuberculosis is an infectious disease with distinctive clinical and pathological features. Tuberculosis occurs in humans and many animal species including species of animals used for production of food (milk or meat) for human consumption (cattle, sheep, goats and deer). *M. bovis* is the causative agent of tuberculosis in animals used for production of food and accounts for a relatively small proportion of human cases. Infection with these microorganisms is chronic and the infected human host may remain entirely asymptomatic or may have mild to moderate illness that does not come to medical attention for long periods. In a proportion of human or animal hosts infected with these microorganisms, the infection may ultimately progress to severe systemic illness. Pulmonary disease is the classical feature and ultimately the disease may progress to death of the host if untreated. Many factors contribute to the persistence of BTB, such as the limitations of diagnostic tests (concerning both sensitivity and specificity), larger herd sizes, increase in animal movements and trade and limited options for control, such as limitations on whole herd depopulation. Therefore, considering current trends associated with BTB control and eradication programs, it is important to increasingly focus resources to target control strategies based on more effective diagnostic methods.

Based on the above conclusions the following recommendations are forwarded:

- Poor management and hygienic practices should be improved
- Sound testing and meat inspection should be implemented
- Public health awareness campaigns should be launched to raise community awareness about the risk of bovine TB transmission through consumption of raw meat.

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REFERENCES

1. Vercoe, J.E., H.A. Fitzhugh and R. Von Kaufmann, 2000. Livestock production systems beyond 2000. Asian-Australian Journal of Animal Sciences 13. Supl S, 411-419.
2. Central statistical agency (CSA), 2013/2014. Population and Housing Census of Ethiopia. Addis Ababa, Ethiopia.
3. Radostits, O.M., C.C. Gay, D.C. Blood and K.W. Hinchelift, 2007. Veterinary Medicine: A Text Book of Disease of Cattle, Sheep, Pig, Goat and Horses. 10th ed. London, UK: Saunders ELSEVIER, pp: 909-918.
4. Romha, G., G. Ameni, B. Gebretsadik and M.M. Gezahegne, 2013. Epidemiology of mycobacterial infections in cattle in two districts of Western Tigray Zone, northern Ethiopia, Addis Ababa University, School of Veterinary Medicine, Debre-Zeit, Ethiopia. African Journal of Microbiology Research, 7: 4031-4038.
5. OIE, 2010. Bovine tuberculosis In Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. Part 2, Section 2.3. Chapter 2.3.3. World Organization for Animal Health.
6. Zinsstag, J., R.R. Kazwala, I. Cadmus and L. Ayanwale, 2006a. Mycobacterium bovis in Africa. In: Thoen C.O., Steele J.H. Gilsdorf M.F. (eds.): Mycobacterium bovis Infection in Animals and Humans. 2nd ed. Blackwell Publishing Professional, Ames, Iowa, USA. pp: 199-210.
7. Ameni, G., A. Ragassa, T. Kassa and G. Medhin, 2001. Survey on bovine tuberculosis and itspublic implications to cattle raising families in Wolaita-Soddo, Southern Ethiopia. Ethiopian Journal of Animal Production, 1: 55-62.
8. Shitaye, J.E., W. Tsegaye and I. Pavlik, 2007. Bovine tuberculosis infection in animal and human populations in Ethiopia: Vet. Med., 8: 317-332.
9. Regassa, A., 2005. Study on Mycobacterium bovis in animals and human in and around Fiche, North Shewa zone, Ethiopia. [MSc. Thesis.] Faculty of Veterinary Medicine, Addis Ababa University, Debre-Zeit, Ethiopia.
10. Bradley, A.J., 2002. Bovine mastitis: an evolving disease. The Veterinary Journal, 164: 116-128.

11. Müller, B., S. Dürr, S. Alonso, J. Hattendorf, C.J.M. Laisse, D.C. Sven, D. Parsons Paul and J. Zinsstag, 2013. Zoonotic Mycobacterium bovis induced Tuberculosis in Humans. Eme Infect Dis., 19: 899-908.
12. Berg, S., E. Schelling, E. Hailu, R. Firdessa, B. Gumi, G. Erenso, E. Gadisa, A. Mengistu, M. Habtamu, J. Hussein, T. Kiros, S. Bekele, W. Mekonnen, Y. Derese, J. Zinsstag, G. Ameni, S. Gagneux, B.D. Robertson, R. Tschopp, G. Hewinson, L. Yamuah, S.V. Gordon and A. Aseffa, 2015. Investigation of the high rates of extra pulmonary tuberculosis in Ethiopia reveals no single driving factor and minimal evidence for zoonotic transmission of Mycobacterium bovis infection. BMCID, 15: 112.
13. Palomino, J., S.le'ao and V. Ritacco, 2007. Tuberculosis in 2007 from basic science to patients care. 1st ed. www. Tuberculosis Textbook.com, pp: 687.
14. Amanfu, W., 2006. The situation of tuberculosis and tuberculosis control economic interest, Tuberculosis, 86: 330-335.
15. Gupte, S., 2006. The short text book of Microbiology. 9thed. JapeeBrathersMedical Publishers Ltd. New Dehi, India, pp: 509.
16. Menzies, F. and S. Neill, 2000. Cattle to cattle transmission of bovine tuberculosis. Vet. J., 160: 92-106.
17. Flynn, J.L. and J. Chan, 2001. Immunology of tuberculosis. Annual Review of Immunology, 19: 93-129.
18. Welsh, M., R. Cunningham, D. Corbett, R. Girvin, J. McNair, R. Skuce, D. Bryson and J. Pollock, 2005. Influence of pathological progression on the balance between cellular and humoral immune responses in bovine tuberculosis. Immu., 114: 101-111.
19. Russ, G.R., 2002. Yet another review of marine reserves as reef fishery management tools.Coral reef fishes: dynamics and diversity in a Complex Ecosystem, pp: 421-443.
20. Dlugovitzky, D., M. Bay, L. Rateni, G. Fiorenza, L. Vietti, M. Farroni and O. Battasso, 2000. Influence of disease survey on nitrate and cytokine production by peripheral blood mononuclear cells (PBMC) from patients with pulmonary tuberculosis (TB). Clin. and Exp. Imm., 122: 343-349.
21. Pollock, J. and S. Neill, 2002. Mycobacterium bovis infection and tuberculosis in cattle. The Vet. J., 163: 115-127.
22. Quinn, P.J., M.E. Carter, K.B. Markey, C.J.W. Donnelly and C.F. Leonard, 2004. Veterinary Microbiology and Microbial Disease of Cattle, Sheep, pigs, goats and horses. 9 th ed. London, UK: Harcourt publishers' Ltd, pp: 918-920.
23. Raghvendra, S.G., A.M. Shankar, S.T. Hedaytullah, A. P. RituKataria, S. Pachpute and Sharma, 2010. Clinical Aspects of Bovine tuberculosis- a chronic Bacterial disease of cattle: an overview. International Journal of Phytopharmacology, 1(2): 114-118.
24. Opara, M.N., N.N. Charles, K.O. Abayomi, A.M. Joy and C.O Ifeanyi, 2012. Prevalence of Bovine Tuberculosis (BTB) in Imo State, Southeastern Nigeria. Journal of Tropical Medical Parasitology, 35: 14-21.
25. Tadayon, K., N. Mosavari and F.M. Mehdi, 2013. An epidemiological perspective on bovine tuberculosis spotlighting facts and dilemmas in Iran, a historically zebudominant farming country. Iranian J. Mic., 5: 1-13.
26. Russel, D.G., 2003. Highlighting the parallels between human and animal tuberculosis. J. Vet. Med. edu. 30: 140-142.
27. Sakamoto, K., 2012. The Pathology of Mycobacterium tuberculosis infection. Vet. Patho., 3: 423-439.
28. Panarella, M.L and R.S. Bimes, 2010. A Naturally Occurring Outbreak of Tuberculosis in a Group of Imported Cynomolgus Monkeys (Macaca fascicularis). J. American ALA Sci., 49: 221-225.
29. Srivastava, K., D.S. Chauhan, P. Gupta, H.B. Singh, V.D. Sharma, V.S. Yadav, Sreekumaran, S.S. Thakral, J.S. Dharamdheeran, P. Nigam, H.K. Prasad and V.M. Katoch, 2008. Isolation of Mycobacterium bovis and M. tuberculosis from cattle of some farms in north India - Possible relevance in human health. Indian J. Med. Res., 128: 26-31.
30. Mahmood, F., A. Khan, R. Hussain and I.A. Khan, 2013. Molecular Based Epidemiology of Bovine Pulmonary Tuberculosis - a Mortal Foe. Pak Vet. J., 2: 185-188.
31. Shitaye, J.E., W. Tsegaye and I. Pavlik, 2007. Bovine tuberculosis infection in animal and human populations in Ethiopia: Vet. Med., 8: 317-332.
32. Ashford, D.A., E. Whitney, P. Raghunathan and O. Cosivi, 2001. Epidemiology of selected mycobacteria that infect humans and other animals, Scientific and Technical Review, OIE. 20: 325-337.
33. Une, Y. and T. Mori, 2007. Tuberculosis as a zoonosis from a veterinary perspective. Comparative Immunology, Microbiology and Infectious Diseases, 30(5-6): 415-425.

34. Decatur, A.L., P. Schnupf and D.A. Portnoy, 2006. Phosphorylation, ubiquitination and degradation of listeriolysin O in mammalian cells: role of the PEST-like sequence. Cellular Microbiology, 8: 353-364.
35. Marais, B.J., W. Brittle, K. Painczyk, A.C. Hesseling, N. Beyers, E. Wasserman, D. van Soolingen and R.M. Warren, 2008. Use of light-emitting diode fluorescence
36. Corner, L.A., D. Murphy and E. Gormley, 2011. Infection in the Eurasian badger (Mycobacterium bovis Meles meles): the disease, pathogenesis, epidemiology ancontrol. Journal of Comparative Pathology, 144: 1-24.
37. Schiller, I., B. Oesch, H.M. Vordermeier, M.V. Palmer, B.N. Harris, K.A. Orloski, B.M. Buddle, T.C. Thacker, K.P. Lyashchenko and W.R. Waters, 2010. Bovine tuberculosis: a review of current and emerging diagnostic techniques in view of their relevance for disease control and eradication. Transboundary and Emerging Diseases, 57: 205-220.
38. COAD, M., R.G. Hewinson, D. Clifford, H.M. Vordermeier and A.O. Whelan, 2007. Influence of skin testing and blood storage on interferon-gamma production in cattle affected naturally with Mycobacterium bovis. Vet. Rec., 160: 660-662.
39. DE LA RUA-Domenech, R., A.T. Goodchild, H.M. Vordermeier, R.G. Hewinson, K.H. Christiansen and R.S. Clifton-Hadley, 2006. Diagnosis of tuberculosis in cattle: a review of the tuberculin tests, gamma-interferon assay and other ancillary diagnostic techniques. Cousins, D.V., Florisson, N.A., 2005. Review of tests available for use in the diagnosis of tuberculosis in non-bovine species. Revue scientifique ET technique, 24: 1039-1059. 81: 190-210.
40. Faye, S., J.L. Moyen, H. Gares, J.J. Benet, B. Garin-Bastuji and M.L. Boschiroli, 2011. Determination of decisional cut-off values for the optimal diagnosis of bovine tuberculosis with a modified IFNgamma assay (Bovigam®) in a low prevalence area in France. Veterinary Microbiology, 151: 60-67.
41. Holmes, J., 2013. An introduction to sociolinguistics. Routledge. Indrigo, J., Hunter, R. and Actor, J. 2002: Influence of trehalose 6, 6’ dimycolate (TDM) during Mycobacterial infection of bone marrow macrophages. MICR, 148: 1991-1998.
42. Medeiros, L.S., C.D. Marassi, E.E. Figueiredo and W. Lilenbaum, 2010. Potential application of new diagnostic methods for controlling bovine tuberculosis in Brazil. Brazilian Journal of Microbiology, 41: 531-541.
43. Zumarraga, M.J., V. Meikle, A. Bernardelli, A. Abdala, H. Tarabla, M.I. Romano and A. Cataldi, 2005. Use of touch-down polymerase chain reaction to enhance the sensitivity of Mycobacterium bovis detection Journal of Veterinary Diagnostic Investigation, 17: 232-238.
44. Cooper, A.M., 2009. Cell-mediated immune responses in tuberculosis. Annual Review of Immunology, 27: 393-422.
45. Anaelom, N.J., O.J. Ikechukwu, E. W.Sunday and U.C. Nnaemeka, 2010. Zoonotic tuberculosis: A review of epidemiology, clinical presentation, prevention and control. Journal of Public Health and Epidemiology, 2: 118-124.
46. Cousins, D.V. and N.A. Florisson, 2005. Review of tests available for use in the diagnosis of tuberculosis in non-bovine species. Revue scientifique ET technique, 24: 1039-1059.