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Bovine Tuberculosis in Ethiopia – A Review On Risk Factors And Its Public Health Importance

Faizullah Peer* and Gizachew Fentahun**

ABSTRACT

Bovine tuberculosis, a chronic infectious zoonotic disease of domestic animals and humans is characterized by formation of granulomas in tissues especially lungs, lymph nodes, liver, intestines and kidneys. Mycobacterium bovis an acid-fast bacterium is the main etiological agent and transmitted both by erogenous and enterogenous routes. In Ethiopia, bovine tuberculosis is endemic and mostly transmitted to humans by ingestion of unpasteurized contaminated milk and close contact with infected animals. Disease causes development of miliary tubercular lesions, chronic cough, and obstruction of air passages, alimentary tract and blood vessels and enlargement of lymph nodes. A spectrum of Cell-Mediated Immune Responses (CMI) predominate infection, projecting the role of macrophages and T-cell populations. In advanced stage, there is increased humoral response. Tuberculin tests; single intra-dermal and comparative intra-dermal tests and other highly sensitive delayed type hyper-sensitivity tests are used for diagnosing tuberculosis (TB) in live animals, TB eradication and also for international trade. Vaccination of calves with attenuated bovine-strain of tuberculosis bacterium, known as Bacillus of Calmette and Guerin (BCG) and testing and culling of infected animals are important measures in bovine tuberculosis (BTB) control and prevention in endemic areas like Ethiopia. Additionally, pasteurization of milk is important before human consumption to reduce public health risks.

Keywords: Tuberculosis, Bovines, Risk factots, Ethiopia.

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Corresponding Author: Faizullah Peer

Email: drpeer7866@gmail.com

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* Professor, Veterinary Medicine, College of Veterinary Medicine, Samara University, Ethiopia.

**Lecturer, College of Veterinary Medicine, Samara University, Afar, Ethiopia.

1. INTRODUCTION

Bovine tuberculosis (BTB) a chronic infectious zoonotic disease of worldwide occurrence is caused by *Mycobacterium bovis*. BTB can have an impact on the ecosystem by transmission of the disease to wild life. It is primarily of economic importance having considerable direct effect on milk and meat production besides animal reproduction (Admassu et al., 2015).

Ethiopia, one among the nations of African continent possesses largest number of bovine population (58 million), has a record of low livestock productivity among other factors is attributed to the low genetic potential and performance, poor nutrition, different diseases, traditional husbandry practices and inadequate skilled manpower, (Akalu., 2017). BTB in Ethiopia is detected on the basis of tuberculin skin testing, abattoir meat inspection and very rarely on bacteriological techniques. A prevalence of BTB ranging from 3.4% (in small holder production system) to 50% (in intensive dairy productions) and 3.5 to 5.2% in slaughterhouses across the country has been recorded (Akalu, 2017). Pasteurization of milk, tuberculin testing followed by culling of infected animals in developed countries has reduced the incidence of disease in humans contrary to the underdeveloped nations of Africa where both human (85%) and animal populations (82%) are inhabitants of prevalent disease or only partially controlled areas (Palmer et al., 2012). This is because of close human-animal interaction and shift from extensive rural production system into the combined urban and peri-urban intensified livestock husbandry practices leading to the transmission of zoonotic diseases (Mbugi et al., 2012)..

Bovines are infected by infected cattle excreting organisms in the exhaled air, sputum, feces (from both intestinal lesions and swallowed sputum from pulmonary lesions), milk, urine, vaginal and uterine discharges, and discharges from open peripheral lymph nodes. Disease can also be disseminated by animals having gross lesions communicating with airways, skin or intestinal lumen and cattle in early stage of the disease before visible lesions. Experimentally infected animals excrete organisms up to 90 days post infection.

Th1-induced cell mediated immunity is triggered by Mycobacterial infection with release of cytokines like tumor necrosis factor-α, Interleukin-12 (IL-12) and interferon gamma (IFN-γ,(insert bracket) essential for macrophage activation. Depending on the quantum of cytokines macrophages may kill and eliminate bacteria or bacteria may lie dormant or disease may develop if bacteria are not controlled by the macrophages (Welsh et el., 2005).

With this background, the different aspects of Bovine Tuberculosis (TB) need to be reviewed.

2. MATERIALS AND METHODS

2.1 Etiology

Mycobacterium is a non-spore forming, nonmotile, obligate aerobic, non-capsular acid-fast bacteria. They are facultative intracellular microbes, thin, rod shaped, slightly curved, measuring 1-10µm in length and 0.2 - 0.6 µm in width having slow generation time of about 15-20 hours. Mycolic acid, a waxy coat lipid enriching cell wall of the mycobacterial cell wall contributes to its acid fastness, hydrophobicity, resistance against many disinfectants, common laboratory stains, antibiotics, physical injuries and slow growth rate by restricting uptake of nutrients. (Birhanu *et al;* 2015)

Mycobacterium bovis is the main etiological agent of bovine tuberculosis, can best survive in frozen tissue. An adverse effect of tissue preservative *i.e*. sodium tetraborate on its viability has been recorded. (Birhanu et al., 2015) though bacteria can survive for various months especially in cold, dark and moist environmental conditions. Survival at 12˚C - 24˚C (54˚F - 75˚F) varies from 18 - 332 days depending on sunlight exposure. From soil or grazing pasture there is infrequent isolation of this organism. Organisms stored artificially can be cultured for approximately two years, remains viable between 4 - 8 weeks in 80% shade. The incubation period of *M. bovis* is 3 weeks (Verma *et al*., 2014).

2.2 Epidemiology

Tuberculosis (TB) a chronic disease of wide range of mammals including humans, cattle, deer, llamas and other wild animals of various age groups are susceptible. Primarily disease affects the cattle, other domestic and wild animals as well as human beings. Disease found throughout the world is more prevalent in Africa, parts of Asia and America, with high rate of prevalence in the tropical and sub-tropical countries (Verma *et al*., 2014). Based on comparative tuberculin skin test, a prevalence of 6.9% of bovine tuberculosis in small holder dairy farms, 12.9% in traditionally managed extensive production systems and 24.6% in intensive dairy farms has been recorded in different areas in Ethiopia (Shitaye *et al*., 2007).

Bovine TB, a globally distributed disease has been eradicated from Antarctica and those countries such as Caribbean islands, parts of South America and Australia by following strict test and slaughter policies, but it is a major health problem in India. Predisposing factors like changing environmental conditions, topography, anthropogenic variables, seasonality, immunosuppression, long antibiotic therapy and working conditions increase chances and severity of infection. Infected cattle are the main source of infection for other cattle, when organisms are excreted in exhaled air,

sputum, feces, milk, urine, vaginal and uterine discharges and discharges from open peripheral lymph nodes (Ameni*et et al*., 2011).
Genetic, behavioral, biological or environmental factors influence epidemiology of bovine TB which have effect on transmission, establishment of infection and expression of disease (Vial *et al*., 2011). Male badgers are more affected as compared to female. Males are at higher risk of mortality promoting gender influence while risking transmission of TB to cattle (Graham *et al*., 2013). It is more prevalent in dairy workers exposed to poor control areas of bovine tuberculosis. The pulmonary form of disease is more severe in occupational groups, working with animals infected with *M. bovis* on farm or slaughter houses, than the alimentary form of disease. Bovine tuberculosis herd prevalence has been positively related with Mycobacterium Tuberculosis Complex (MTC) is also correlated positively with size of land, number of imported cattle and presence of wild host but not with isolation of cattle as well as density of cattle. Hereditary and maternal influences have a great role in the incidence of TB in cattle progeny. (Verma *et al*., 2014) besides factors associated with tuberculosis influencing the occurrence of disease such as sex, breed and social management of livelihood conditions (Acevedo *et al*., 2013).

2.3 Transmission

Bovine tuberculosis caused by *M. bovis* is a zoonoticdiseases in which both natural and anthropogenic movement of animals has influenced the epidemiology (Kruse *et al*., 2004). In many parts of the world, badgers, brush-tail opossums, wild boars, deer and other wildlife species constitute a wildlife reservoir of the pathogen. Thus, the natural movement of these reservoir animals increases the spread of the disease to domestic animals and thereby, its public health impact.
Transmission of *M. bovis* can occur between animals, from animals to humans and vice versa and rarely, between humans. *M. bovis* infection is transmissible from cattle to humans directly by aerogenous route and through direct contact with materials contaminated with nose and mouth secretions from an infected herd of cattle. Research findings revealed that individuals at risk are persons directly in contact with potentially infected animals such as veterinarians, abattoir workers, meat inspectors, autopsy personnel, farmers, milkers, animal keepers, animal dealers, laboratory personnel and owners of potential tuberculous pets (e.g. monkeys) (Yumi *et al*., 2007) (missing in references). Indirectly, man acquires the disease from animal sources by ingestion of meat and meat products from slaughtered infected cattle and consumption of unpasteurized infected milk.

2.4 Clinical signs

TB a chronic debilitating disease occurs in cattle. No symptoms occur in the early stage of disease. However, in late stage, there is progressive emaciation, a mild fluctuating fever, weakness and inappetence. When infection is present in the lung, then dyspnoea, moist cough or tachypnoea may occur. In the terminal stage, animals become extremely emaciated and develop acute respiratory distress. Involvement of respiratory tract and its role in pathogenesis

of disease is evidenced by the predominant distribution of lesions present in upper respiratory tract, lung and tonsils in affected human as well as in animals (Van Rhijn *et al*., 2008).
Some cows with extensive miliary tubercular lesions are clinically normal but in most cases progressive emaciation unassociated with other clinical signs occur, in spite of good appetite. A capricious appetite and fluctuating temperature are commonly associated with disease. The hair coat may be rough. Affected animals tend to become more docile and sluggish but eyes remain bright and alert. These general signs often become more pronounced after calving. Pulmonary involvement is characterized by chronic cough due to bronchopneumonia. Cough occurs only once or twice at a time and is low, suppressed and moist which is easily stimulated by squeezing the pharynx or by exercise and is most common in morning and in cold weather (Van Rhijn *et al*., 2008).
In advanced cases, air passages, alimentary tract, or blood vessels may be obstructed by enlargement of lymph nodes. Lymph nodes of the head and neck may become visibly affected and sometimes rupture and drain. Involvement of the digestive tract is manifested by intermittent diarrhoea and constipation in some instances (Van Rhijn *et al*., 2008).
There may be chances of bloat occuring due to pressure of enlarged mediastinal glands on the oesophagus. The enlargement of retropharyngeal glands results in dysphagia. Extreme emaciation and acute respiratory distress may occur during the terminal stages of tuberculosis. Lesions on the female genitalia may occur, while male genitalia are seldom involved. Tuberculosis mastitis is of major importance because of danger to public health and of spread of disease to claves and difficulty of differentiating it from other forms of mastitis (Radostits *et al*., 2000).

2.5 Associated risk factors

2.5.1. Risk factor for cattle

Animal level risk factors are cattle breeds, genetic resistance, physiological state of the animal, age, sex, stress, concurrent infection, immune status and body condition score (BCS) (Elias *et al*., 2008). Several past and recent studies have shown that susceptibility to bovine TB can vary between cattle breeds with suggestions that indigenous zebu cattle are more resistant to BTB than exotic breeds (Zeru *et al*., 2014). This fact is substantiated by the lower prevalence recorded in several studies and it is evident where European breeds of cattle have been used to establish a dairy industry. Genetically improved cattle may suffer more severely from deficient housing and malnutrition and thus be more prone to infection (Gebrez gabiher *et al*., 2014).
Studies conducted in different areas of our country also confirm variation in susceptibility to bovine TB among cattle breeds (Elias *et al*., 2008). Risk factors at herd level are herd size, types of farming practice and housing of cattle, geographical origin, history of bovine TB in the herd and human antecedent of tuberculosis in the household, contact between animals and with wildlife reservoirs, introduction of cattle in a herd, herd movements and trading, lack of performance of diagnostic tests, the use of hired/ shared bulls, manure and environmental persistence of *M. bovis* (Gumi *et al*., 2012). In Ethiopia, as wildlife habitats are not fenced, there is intensive interaction between a fast-growing human population and livestock and wildlife competing for scarce grazing land. Wildlife and, in particular, herbivores sharing pastures with cattle

might therefore be at risk for bovine TB transmission. Domestic animals were sharing grazing land in close proximity with wildlife in the area where wild animals live (Mamo *et al*., 2013).

2.5.2. Risk factors for human

Consumption of raw milk and meat in Ethiopian societies, a habit traditionally accepted is the main risk factor for *M. bovis* infection in humans (Namomsa *et al*., 2014) as *M. bovis* has been detected from raw milk confirming the existing problem and the potential risk of the infection in humans. Moreover, poverty, malnutrition, HIV infection, illiteracy, the consumption of raw milk (unpasteurized milk), uncooked or poorly cooked meat, work condition and close contact to livestock and using cow dung for plastering wall or floor are the main risk factors which contribute to the acquisition *M. bovis* infections in both urban and rural human populations in Ethiopia (Otte *et al*.,2002). Because of these factors cases of human TB of animal origin will continue to pose a serious public health problem, especially in areas where raw milk or its products are commonly consumed (Namomsa *et al*., 2014).

Intensification of livestock production has promoted close physical contact between the owner and his cattle, especially at night and thus facilitates the transmission of bovine TB and in turn intensifies TB as zoonosis. Moreover, there is habit of chewing and spitting tobacco to their cattle among Ethiopian farmers. These factors have increased risk of transmission for *M. tuberculosis* as well as for *M. bovis* at the human–livestock interface through inhalation of cough spray. (WHO, 2012).

2.6 Diagnosis

2.6.1. Acid-Fast Staining

Acid fast staining is commonly used to detect Mycobacteria in clinical samples by zeil-Neelsen or fluorescent staining for the diagnosis of Bovine TB and to monitor treatment progress. The lipid content ranging from 20-40% of the dry weight, in the cell wall of the acid-fast bacteria including *M. Bovis*, enables these organisms to resist decolorization with acidified organic solvents. They take up this stain only and appear as short red or pink rods on microscopic examination (*Sharma et al*; 2005).

Primarily, from the TB suspected tissues proper stained smears are made for preliminary examination. Smear made on a grease free clean slide from scrapings of cut surface tissue is air dried and fixed on flaming for one or two seconds, is treated with concentrated carbol fuchsin by heating and finally decolorized with a sulfuric acid and alcohol solution. Malachite green or methylene blue is commonly used as a counter stain (Birhanu *et al*., 2015). The stained smears are examined under an ordinary light microscope for the presence of acid-fast bacilli., The bacteria appear as red, colloidal or bacillary cells, 1-3 microns in length, as single rods or in clumps (WHO, 2013).

2.6.2. Culturing

Mycobacteria can be isolated by culture on an egg based media, Lowenstein-Jensen (LJ) medium. *M. bovis* has sparse, thin growth on glycerol containing media that is

called dysgenic, however, it grows well on pyruvate containing media without glycerol (Patterson and Grooms, 2000).

2.6.3. Tuberculin Test

Tuberculin testing is the standard method used internationally for the detection of bovine tuberculosis where intra-dermal injection of bovine tuberculin as purified protein derivative (PPD) is given in the mid neck region or in the skin of the caudal fold in single intra- dermal testing, SID, after the preparation of the site properly. The results are recorded by observing a swelling (a delayed hypersensitivity reaction at the site) 72 hours later. Comparative intra-dermal testing can also be performed by the same procedure where PPD and avian tuberculin is given intra-dermally at two different sites in the mid neck region or skin of the caudal fold. followed by observing a swelling at the site of injection. However, higher doses of tuberculin may be used in the caudal fold because skin of the neck is more sensitive than caudal fold (OIE, 2009).

Swelling at the site of injection or delayed hypersensitivity reaction can be noticed after 3-6 weeks in an animal or herd who had been very recently in contact with infected animals to avoid the probability of false negatives. SID cannot be used in the eradication of bovine TB as the sensitivity of the test is less than 100%. Tuberculin test becomes non responsive in chronically infected animals with severe pathology should also be considered. The tuberculin test has not been well validated in most non-bovid and non-cervid species (OIE, 2009)

2.6.4. Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA, helpful in anergic cattle and deer, is a suitable antibody-detection test and can be a complement, rather than an alternative, to tests based on cellular immunity. It has an advantage of its simplicity, but it is less sensitive mostly because of the late and irregular development of the humoral immune response in cattle during the course of the disease. It is poor in specificity, is also poor in cattle when complex antigens such as tuberculin or *M. bovis* culture filtrates are used. However, a comparison of antibody levels to PPD-B and PPD-A has been shown to be useful in increasing specificity in the ELISA (Chambers, 2013).

However, using a combination of different antigens including proteins, improvement may be possible. The test is also helpful for *M. bovis* infections in wild life. This test is now used for elephants and non-human primates in the USA and is approved for use in badgers by United Kingdom (Lyashchenko *et al*., 2004).

2.7 Treatment

Isoniazid, combination of streptomycin and para-aminosalicylic and other acids are commonly practiced in human tuberculosis whereas in animals it is not a favorable option for the treatment or eradication of the disease especially in developed countries and is not economical. The disease requires long term therapy and the therapeutic regimen is not followed judiciously in animals, chances of development of multidrug resistant (MDR), extremely drug resistant (XDR) and even totally drug resistant (TDR) bacterial strains becomes obvious. Vaccination of calves with BCG and testing and culling is the viable option for prevention and eradication of tuberculosis (Verma *et al*., 2014).

Bacillus Calmette Guérin (BCG) vaccine is the most popular and effective vaccine against TB in humans and has an advantage for its use in cattle since the vaccine is safe, inexpensive and is commercially produced for human application on a large scale. The vaccine has shown variable levels of efficacy, protecting humans against pulmonary TB in children and adults, ranging from 0% - 80% (Parlane and Buddle, 2015). However, in animals vaccination with BCG sensitizes animals to the tuberculin skin test, and vaccinated animals will therefore, exhibit false positive results in classical skin test for a significant period after vaccination. Therefore, test and slaughter based control strategies using tuberculin skin testing is a favored option over BCG vaccination in many countries including Ethiopia (Ameni *et al*., 2010).

2.8. Control and Prevention

Tuberculosis a zoonosis, causes severe loss of productivity in infected animals needs to be prevented and controlled. However, control measures are not applied or are applied inadequately in most developing countries because of financial constraints, dearth of trained professionals and lack of political will. Moreover, in both the animal and public health sectors of national governments and donor agencies underestimate the importance of tuberculosis as zoonotic disease. Standard public health measures should be applied to manage patients with contagious *M. tuberculosis* to stop person-person transmission (Theon *et al*., 2009). Due to the limitations in the treatment of tuberculosis in animals, cattle should not be treated at all and farm animals suffering from tuberculosis must be slaughtered (culled). Moreover, *M. bovi*s is resistant to pyrazinamide, a drug widely used in the treatment of human tuberculosis caused by M. tuberculosis Complex (Krauss *et al*., 2003).

3. CONCLUSION AND RECOMMENDATIONS

Conclusions.

1 Tuberculosis is a zoonotic disease transmissible to human beings and extra pulmonary TB including BTB remains a significant problem in under developed countries.

2 Disease transmission, a most important factor in the spread of tuberculosis among humans, is mainly because of traditional drinking of raw milk without pasteurization and meat and is the chief source of dissemination besides aerosol transmission. Educate people about pasteurization infrastructure and public health importance and the hazards of raw milk consumption.

3 Antimicrobial therapy in animals is not a favored option because of limitations of longterm treatment and resistance to drugs. Culling of infected animals by test and slaughter and strict meat inspection at slaughter houses is the only means of disease eradication in animals.

4 Conducting intensive surveillance programs including on-farm visits, individual testing of cattle systematically including infected as well as in contact animals, quarantine, controlled movement of infected animals and their removal.

5 Advancement in the diagnostics comprising of conventional, immunological and molecular techniques and vaccine development has revolutionized the detection and control of TB in humans and domestic and wild animals as well, especially bovines. This can be a better option in the control and eradication of the disease.

Based on the above conclusions, the following recommendations are forwarded

- A Calves born from known TB dams should be separated to avoid transmission of the tuberculosis through infected milk.
- T B Test positive animals should be culled and is important that calves being reared as herd replacements be fed on tuberculosis-free milk, either from known TB free animals or pasteurized milk.
- C Infrastructure for pasteurization should be developed and pasteurized milk should be supplied for public consumption.
- D People around country should be educated about public health importance and the hazards of raw milk and meat consumption.
- E Vaccination against tuberculosis should be made mandatory for humans and animals because of zoonotic nature of the disease.
- F Bio-security measures and protective clothing should be worn to minimize interaction between domestic animals and wildlife animals during handling of the diseased animal and infected carcasses.
- G Carcass of infected animals should be disposed as per law of the state preferably, buried deep under the ground.

Abbreviations

BTB……. Bovine tuberculosis

CMI…….. Cell-Mediated Immune responses

BCG……. Bacillus of Calmette and Guerin

TB……. Tuberculosis

M.bovis……. Mycobacterium bovis

OIE……. Office of de epizootic

WHO…… World Health Organization

AFB…… Acid fast bacilli

IL…… Interleukin

IFN-γ……Interferon gamma

ZN……Ziel-Neelsen

PPD…… Purified protein derivative

IU…… International Units

ELISA…… Enzyme-Linked Immunosorbent Assay

ML…… Milliliter

USA…… United States of America

USDA…… United States drug and administration

HIV…….. Human immune virus

MDR…… Multidrug resistant

XDR…… Extreme drug resistant

TDR…… Totally drug resistant

MTC…… Mycobacterium Tuberculosis Complex

BCS…… Body condition score

AIDS…… Acquired immune deficiency diseases

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