Review on Bovine Tuberculosis

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SUMMARY: Bovine tuberculosis (BTB) is a chronic granulomatous disease of cattle caused predominantly by *Mycobacterium bovis (M. bovis)*. The disease is transmitted between animals primarily by inhalation although transmission through ingestion is also common in cattle grazing on pasture contaminated with *M. bovis*. The disease causes significant animal health-induced economic loss, and its impacts include reduction in productivity, movement restrictions, screening costs, culling of affected animals, and trade restrictions. *Mycobacterium bovis* is an intracellular, non-motile, facultative, weakly Gram-positive acid-fast bacillus which belongs to the Mycobacterium tuberculosis complex. The pathogen affects all age groups of susceptible hosts of domestic, wild animals and human. In Ethiopia, bovine tuberculosis is endemic and mostly transmitted to humans through ingestion of unpasteurized contaminated milk and contact with infected animals. Tuberculinization test, single intradermal test and comparative intradermal test, is the valuable delayed type hyper sensitivity test used for diagnosing TB in live animal, and used in TB eradication and 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 are important measure in BTB control and prevention endemic area like Ethiopia. It is important to pasteurize milk before human consumption to reduce public health risk.

Keywords: *Bovine, Mycobacterium bovis, Tuberculosis*

INTRODUCTION

Mycobacterium bovis (M. bovis) is the causative agent of bovine tuberculosis (BTB) and belongs to the *Mycobacterium tuberculosis* complex (MTC) of bacterial strains [1]. The MTC is a group of genetically very closely related pathogens, which can cause tuberculosis (TB) disease with similar pathology in a variety of mammalian species [2]. The most prominent member of the MTC is *Mycobacterium tuberculosis (*MTB*)*, the principle causative agent of TB in humans, causing each year more than 1.5 million deaths and having experienced a recent re-emergence through the advent of extended forms and the appearance of multi drug resistant strains. Other members of MTC are *M .tuberculosis, M. bovis, M. africanum, M. canettii, M. microti, M. caprae- M. orygis, M. suricattae,* and lastly recognized *M. mungi* [3].

BTB is a chronic, generally respiratory disease, which is clinically difficult to diagnose although emaciation, loss of appetite, chronic cough and other signs of pneumonia could be symptoms developing at relatively late stages of the infection in cattle [4]. Especially in developing countries, clinical forms of many other chronic, emaciating diseases, like African trypanosomiasis, chronic contagious bovine pleuropneumonia (CBPP) or chronic multiparasitism, are difficult to be distinguished from BTB. BTB pathology is characterized by the formation of granulomatous lesions, which can within the course of the disease regress or exhibit extensive necrosis, calcify or liquefy and subsequently lead to cavity formation. During meat inspection, procedures on cattle carcasses in slaughter houses, TB lesions are primarily found in the upper and lower respiratory tract and associated lymph nodes [5]. However, the bacteria can also develop a systemic infection, disseminate within its host and affect other organs [6]. *M. bovis* is a slow growing, facultative intracellular, aerobic and gram-positive bacterium with a dysgonic colony shape

when cultured on Löwenstein-Jensen (LJ) medium [7]. As all *Mycobacterium* spp., *M. bovis* has an unusual cell wall surface structure characterized by the dominant presence of mycolic acids and a wide array of lipids [8]. This waxy lipid envelope confers an extreme hydrophobicity, which renders the bacteria acid and alcohol fast, a feature that can be exploited to identify mycobacteria via the Ziehl-Neelsen staining technique [9].

The existence of BTB in Ethiopia first reported in 1960s based on detection of tuberculous lesions in cattle at slaughterhouse [10]. Until very recently, that much of the information regarding the status of BTB in different regions of Ethiopia emanates from recording of lesions at abattoirs and skin test result in different part of the country. Since then pathological findings including BTB lesions have compiled from major abattoirs and reports sent monthly and annually to the meat inspection and quarantine division of the Ministry of Agriculture. Zoonotic TB is an important public health concern worldwide, especially in developing countries, because of deficiencies in preventive and/or control measures[11]. In developed countries, the disease has almost been eradicated after the implementation of preventive and control measures such as testing, culling or pasteurization of milk. Since BTB remains a worldwide problem, it is imperative to intensify control and preventive measures aimed at its eradication. The incidence of *M. bovis* in humans probably remains underestimated, as a distinction between the mycobacterial species, i.e. *M. bovis* and MTB, is not systematically performed. Since the real incidence of *M. bovis* in human health is still unknown, it is essential to advance the eradication of BTB worldwide by means of adequate programmes, especially in developing countries [12].

TB in human caused by MTB and *M. bovis* is indistinguishable clinically, radiologically and pathologically [13]. Humans often acquire infections through inhalation of aerosols or consumption of contaminated milk and possibly meat. The World Health Organization's (WHO) "END-TB" goal is to eliminate all forms of human TB as a public health problem by 2035. However, the contribution of zoonotic TB to human TB is poorly described, particularly in sub-Saharan Africa, where a combination of endemic bovine BTB evolving human-animal interfaces (e.g. expanding dairy production and increasing global animal-based protein consumption) [14].

The main objectives of this seminar are:
* ❖ To review the zoonotic importance of bovine tuberculosis

* ❖ To review on mitigation, prevention and control, and the economic significance of this important disease.

BOVINE TUBERCLOSIS

Bovine tuberculosis has long been reported in Ethiopian cattle populations [15]. Transmission of Bovine TB can be either direct, through close contact between infected and susceptible individuals, or indirect from exposure to viable bacteria in a contaminated environment. Respiratory and alimentary or oral routes are routes of infection where transmission between cattle is mostly thought to occur by inhalation of contaminated aerosol [16]. Infection can also occur via the gastro-intestinal tract when animals ingest contaminated food, water, soil or milk. Cutaneous, genital, and vertical (congenital) transmissions have been seen but are rare [17]. The disease can also transmitted indirectly through infected flightless vectors, winged vectors or mechanical vectors. Nowadays there are a number of diagnostic tests available to detect *M. bovis* in cattle. In Ethiopia, detection of Bovine TB is carried out most commonly based on the tuberculin skin testing, abattoir meat inspection and very rarely on bacteriological techniques [15].

Mycobaterium bovis multiplies quite slowly and also there are usually low in number. These make *M. bovis* hard to detect either directly in clinical sample from live animals or by growing it in the laboratory organisms in clinical sample. Therefore techniques looking directly for the organisms or its DNA, such as culture or polymerase chain reaction (PCR), are insensitive. Hence, primary diagnostic tests for *M. bovis* rely on detecting the immune response of the host to the organism using skin tests and gamma interferon [2]. Single intradermal tuberculin skin test (SIDT) and comparative skin test (CIDT) remain the international field diagnosis methods of Bovine TB. The skin test is the central ante mortem diagnostic test applied to the diagnosis of tuberculosis in cattle. Pivotal for the intradermal skin test are the purified protein derivative (PPD) tuberculins. Tuberculin skin test is based upon the measurement of a delayed type hypersensitivity response to intradermally injected tuberculins [18].

The cellular response, the pathology and clinical signs seen with the disease on cattle are associated with the body's immune response to the bacteria and not solely with the pathogenicity of the bacteria itself [2]. Both SIDT and CIDT are typically performed either in the neck or caudal tail fold. The decision which test to apply is influenced by a variety of considerations which include the prevalence of disease and the exposure of cattle to other mycobacteria. Although CIDT has more specificity

and sensitivity than SIDT, these tests seem to lack sensitivity [18]. Sensitivity depends on the potency and dose of tuberculin administered, the post infection interval, desensitization, postpartum immune suppression and observer variation and the estimates of the sensitivity of tuberculin tests ranged from 68 to 95% [4].

Etiology

Mycobacterium bovis is the main etiological agent of bovine tuberculosis. It is found that *M. bovis* best survive in frozen tissue and there is adverse effects of tissue preservative *i.e*. sodium tetraborate on viability. In the environment *M. bovis* can survive for various months especially in cold as well as dark and conditions which is moist. The survival period varies from 18 - 332 days at 12˚C - 24˚C (54˚F - 75˚F) which is dependent of sun light exposure. From soil or grazing pasture there is infrequent isolation of this organism. It has been found that culture of the organism can be done for approximately two years in samples that are stored artificially. The viability of the organism has been found more recently to be between 4 - 8 weeks in 80% shade whereas it can get destroyed in either summer or winter on New Zealand pastures. The incubation period of *M. bovis* is 3weeks [19].

Epidemiology

Tuberculosis (TB) is chronic disease in nature affecting a wide range of mammals that include: humans and cattle, deer and other wild animals. All species including humans with various age groups are susceptible. The bacteria primarily affect the cattle and other domestic and wild animals as well as human being. Disease is found throughout the world but more prevalent in Africa, parts of Asia and America. The prevalence of disease is high in the tropical and sub-tropical countries [20].

Sources of Infection and Ways of Transmission

Bovine Tuberculosis can be transmitted in various ways. For instance in air that is exhaled; sputum and urine, feces as well as pus the bacteria can spread. Either direct contact or contact with infected animal excreta, aerosol inhalation can spread the disease that depends on the involvement of the species [21]. The common mode of transmission is inhalation or ingestion. Aerogenous or inhalation: it is mainly by droplet infection, inhalation of dust contaminated by sputum, faeces, urine of infected animals.

Clinical Signs

TB is usually a chronic debilitating disease in cattle, but it can occasionally be acute and rapidly progressive. Early infections are often asymptomatic. In countries with eradication programs, most infected cattle are identified early and symptomatic infections are uncommon. In late stages, common symptoms included progressive emaciation allows grade fluctuating fever, weakness and in appetence. Animals with pulmonary involvement usually has cough that is worse in the morning, during cold weather of exercise and may have dyspnea ortachypnea. In terminal stage, animals may become extremely emaciated and develop respiratory distress. In the final stage of the disease, animals become disoriented, can't climb, and may be seen wandering about in day light [22, 23].

Pathogenesis

The bacteria usually enter the respiratory system of a cow and settle in the lungs. Macrophages in lungs are then responsible for phagocytizing the organism. The organism replicates intracellularly after it has been taken up by the macrophages. A granuloma or tubercle forms as the body tries to wall off the infected macrophages with fibrous tissue. The infection can spread hematogenously to lymph nodes and other areas of the body and cause smaller, 2 - 3 mm in diameter, tubercles. The formation of these smaller tubercles is known as "miliary tuberculosis" [24].

Postmortem Lesions

TB is characterized by the formation of granulomas (tubercles) where bacteria have localized. These granulomas are usually yellowish and either caseous, or calcified, they are often encapsulated. Some tubercles are small enough to be missed by the naked eye unless the tissue is sectioned. In cattle, tubercles are found in the lymph nodes, particularly those of the head and thorax. It is common in the lungs, spleen, liver and the surfaces of body cavities [25]. In disseminated case, lesions are sometimes founds on the female genitalia, but are rare on the male genitalia. In countries with good control programs, infected cattle typically have few lesions at necropsy. Most of those lesions found in lymph nodes associated with the respiratory system. However, small lesions can often be discovered in the lungs of these animals if the tissues are sectioned [19].

Diagnosis

Although the presumptive diagnosis of TB is often based on clinical suspicion and radiological data, a definitive diagnosis of the disease requires microbiological assays. Laboratory diagnosis of TB has been based on smear microscopy, culture and phenotypic identification. While the quickest, easiest and cheapest method available is acid-fast staining, its low sensitivity (45% - 80% of positive cultures) has limited its usefulness, especially in geographical areas of lower incidence, in BTB [26].

Treatment

In human tuberculosis, drugs like isoniazid, combinations of streptomycin and para-aminos alicylic and other acids are commonly used. The treatment of animals with tuberculosis is not a favored option in eradication conscious countries and is not economical. Long term therapy requirement of the disease can create the chances of development of multidrug resistant (MDR), extremely drug resistant (XDR) and even totally drug resistant (TDR) bacterial strains if treatment regime is not properly followed. So that vaccination of calves with BCG and testing and culling is important for prevention and eradication of tuberculosis [19]. Bacillus Calmette and Guérin (BCG) vaccine is the only TB vaccine licensed for use in humans and has advantages for use in cattle since the vaccine is safe, inexpensive, is commercially produced for human application.BCG vaccine has variable levels of protection efficacy in humans against pulmonary TB in children and adults, ranging from 0% - 80% [27]. However, in animals vaccination with BCG sensitizes animals to the tuberculin skin test, and vaccinated animals will therefore, at least for a significant period post vaccination, become test positive in the classical skin test. For this reason, test and slaughter-based control strategies based on tuberculin skin testing were favored above BCG vaccination in many countries including Ethiopia [28].

ECONOMIC IMPORTANCE

Tuberculosis occurs in almost every country of the world and is of major importance in dairy cattle due to high morbidity and loss of production as infected animals lose 10% - 25% of their productive efficiency. Apart from these, advance tuberculosis may lead to death of the animals. WHO declared tuberculosis as global emergency [29]. About one third of human populations of the world are suffering from tuberculosis infection [20]. Tuberculosis has great importance regarding the economy of the livestock industry because it can infect the human population due to its zoonotic nature; therefore it is an important public health issue [16]. It is listed disease by World Organisation for Animal Health formerly Office International des Epizootics (OIE). Tuberculosis also has significance to the international trade of animals and animal product [30].

PUBLIC HEALTH RISKS

Human tuberculosis due to *M. bovis* is usually underestimated or under diagnosed because of no clinical, radiographical and histopathological differentiation of tuberculosis caused by *M. tuberculosis* and *M. bovis* [31]. *M. bovis* is not the major cause of human tuberculosis but it can infect human beings too either by consuming raw milk, meat and their products from infected animals [32], or by inhaling infective droplets or direct exposure to infected animals [19]. In an estimate, about 10% cases of human tuberculosis are caused by *M. bovis*, while majority are caused by *M. tuberculosis* [31]. In countries where in milk is pasteurized and there is effective implementation of bovine tuberculosis program, tuberculosis in human due to *M. bovis* is very rare. But in areas where the disease in bovine is poorly controlled the reporting of the disease is more frequently done. In farmers as well as abattoir workers and others the incidence rate is higher. Exposure to other species apart from cattle can cause infection in human. It has been documented that goats as well as seals, farmed elk and rhinoceros can also act as sources of bovine tuberculosis. A source of infection may be wildlife especially in countries where people use to take bush meat [11]. If the whole carcass is condemned then it indicates a high degree of tuberculosis infection and its transmission so it requires immediate attention from both the economic and public health point of view [33]. Being cause of chronic granulomatous disease tubercle bacilli increases susceptibility to bladder and lung cancer. Though BCG induced cytotoxicity of bladder has paved the way towards initiation of BCG immunotherapy for treatment of bladder cancer [34].

CONTROL AND PREVENTION

Tuberculosis needs to be prevented and controlled because it causes loss of productivity in animals infected; there is risk of infection to humans [35]. However, because of financial constraints, scarcity of trained professionals, lack of political will, as well as the underestimation of the importance of zoonotic tuberculosis in both the animal and public health sectors by national governments and donor agencies, control measures are not applied or are applied inadequately in most developing countries [36]. Standard public health measures used to manage patients with contagious *M. tuberculosis* should be applied to contagious patients with *M. bovis* to stop person-person transmission [37]. Cattle should not be treated at all and as such farm animals with tuberculosis must be slaughtered (culled). This is due to the fact that *M. bovi*s is resistant to pyrazinamide, which is widely used in the treatment of infections caused by M. tuberculosis Complex in humans [38]

The methods of controlling *M. bovis* in wildlife are limited and dependent on sound disease control principles and judicious use of diagnostic tests. Though population control and vaccination are potential alternative control methods but not applicable in all the situations:

- Slaughter of diseased cattle can be an effective policy for tuberculosis eradication, if no other reservoirs of infection are maintained in near surroundings.
- In early stage of disease, test and segregation method is followed while in later or terminal stage of disease, test and slaughter method is recommended.
- The animal which is import from other state or country should be strictly quarantine.
- Post mortem examination, meat inspection, intensive surveillance, gamma interferon assay, systematic individual testing of animals, followed by removal of infected and in contact animals for reducing or eliminating the disease .
- Ancillary diagnostic techniques, herd testing, health surveillance, ante mortem diagnosis including tuberculin testing and immunization are effective in controlling the TB incidences.
- Hygienic measures to prevent the spread of infection should be instituted as soon as the first group of reactors is removed. Feed troughs should be cleaned and thoroughly disinfected with hot, 5% phenol or equivalent cresol disinfectant. Water troughs and drinking cups should be emptied and similarly disinfected.
- Monitoring of the control and eradication programme should be done continuously to know the progress of the programme and for the implementation of necessary modification as required to the programme. Application of advanced genotyping tools and co-operation and co-ordination in human as well as veterinary health care professionals will ultimately help in eradication of bovine tuberculosis especially in developing nation like India [19].

CONCLUSION AND RECOMMENDATIONS

The spread of tuberculosis from animals to humans in developing countries mostly from infected milk is a serious means of transmission that is being ignored. Milk pasteurization before human consumption is very important, rural dwellers should be educated on the need to boil milk before consumption since they lack infrastructures for pasteurization. Extra pulmonary TB including BTB remains a significant problem in low-income countries and there is a diagnostic challenge in developing countries, where a high rate of HIV infection found. The disease has an important public health issue due to its zoonotic significance. In certain species of animals, antimicrobial treatment has been attempted but as long term treatment is required so in eradication conscious countries practicing anti-tubercular treatment is not a wise option. Programs involving eradication of the disease consists of inspection of meat at post mortem and conducting surveillance program intensively. This includes, on-farm visits, individual testing of cattle systematically along with infected as well as in contact animals' removal and control of movement.

Based on the above conclusion the following recommendations are forwarded:

- It is important that calves being reared as herd replacements be fed on tuberculosis-free milk, either from known free animals or pasteurized.
- Vaccination against tuberculosis should be supplied for humans and animals as it is zoonotic disease
- Bio-security measures should be followed on herd/farm which helps in decreasing or reducing the interaction between domestic animals and wildlife animals
- The animal which is import from other state or country should be strictly quarantine
- Pasteurization of milk of before consumption.
- Strict meat inspection should be carried out officially by trained personal
- Treatment of infected animals is not economically feasible because of the high cost, lengthy time and the larger goal of eliminating the disease, so the infected animal should be tested and culled.
- Educational and technical assistance should be provided by developed countries to promote control of tuberculosis.

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