Growing Significance of *Mycobacterium bovis* in Human Health

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ABSTRACT

Tuberculosis is one of the most wide spread highly infectious bacterial zoonotic diseases, and is responsible for high morbidity and mortality in the world particularly in the developing nations. *Mycobacterium bovis* and closely associated acid fast bacilli cause disease in humans and animals. Humans can be infected with *M. bovis* where cattle act as the principal reservoir. Air borne infections continue to occur among the persons working in the meat industry, slaughterhouses, and in persons living in close physical contact with infected animals.*M. bovis* infection is recognized as an occupational hazard to abattoir workers, livestock handlers and veterinarians. The main cause of concern related to *M. bovis* in industrialized counties are epizootics nature of the disease in domesticated and wild animals. In addition, latent infection in immigrants particularly in HIV infected patients are also a big issue in developed world, since those people could be the potential source of TB for other people. The reemergence of *M. bovis* infection in captive and free-ranging wild animals, with subsequent transmission to domestic animals, is of concern to livestock producers and regulatory officials. As wild animals represent major reservoir of tuberculosis bacilli, it is imperative to investigate the role of wild animals in transmission dynamics of *M. bovis* infection. Further studies on the molecular epidemiology and development of safe, cheap and potent drugs to mitigate tuberculosis in highly susceptible population particularly in HIV/AIDS patients is emphasized. In addition, multidisciplinary approaches such as 'One Health' that comprise professionals from medical science, veterinary medicine and wildlife etc. are essential to take measures to control this devastating bacterial zoonosis.

Introduction

Tuberculosis (TB) is one of the oldest classic bacterial zoonoses, and is the leading cause of death due to single infectious agent among the adults in the world (Pal, 2005).Approximately, one-third of the world population is affected with TB (Pal, 2007). In 2012, about 8.6 million people fell ill with TB and 1.3 million died from TB (WHO, 2011).Among these population Africa displaying the highest annual risk of infection by TB, probably catalyzed by the AIDS/HIV pandemic (Corbett *et al*., 2003). Pulmonary TB occurs in 74-100% of patients with HIV infection (Pal, 2005).

Mycobacterium bovis is the most universal pathogen amongst the *Mycobacterium* affecting many vertebrates including humans of all age groups although cattle, goats and pigs are found to be most susceptible (Radostits *et at*., 2000; Pal and Boru, 2012). Bovine tuberculosis (BTB) caused by *M. bovis* is a chronic infectious disease of animals characterized by the formation of granulomas in various organs, more significantly in the lungs, lymphnodes, intestine and in the kidneys (Pal and Boru, 2012).

BTB is one of the important diseasethat affects theproduction of animal. The human infections due to *M. bovis* have been reported from many countries of the world (O'Reilly and Daborn, 1995; Grane, 2001, Jou *et al.*, 2008; Pal and Boru 2012). BTB is caused by *M.bovis*, which is genetically related to *M. tuberculosis*, the causative agent human tuberculosis (HTB). It could be speculated that BTB in humans is becoming increasingly important in developing countries as humans and animals are sharing the same micro-environment and dwellingpremises, especially in rural areas. Presently, the role of *M.bovis* as a cause of human tuberculosis is becoming significant especially in developing countries where there is a high prevalence of HIV/ADIS (Amanfu, 2006). The etiologic significance of *M.bovis* inHTBhas been undermined because of the following reason in most developing countries; bacteriological diagnosis of pulmonary tuberculosis usually relies on the acid-fast bacillus (AFB) smear examination due to limited laboratory resources. Use of culture is generally reserved for special situations, such as suspected treatment failure and relapses. In addition, culture is used in special surveys, including those undertaken to measure the prevalence of drug resistance (Sequeira*et al*., 2005).

Infection of human due to *M.bovis* is mainly through drinking of raw milk and hence BTB due to *M. bovis* does occur in extra-pulmonary from particularly in cortically lmphadenitis form. However, *M. bovis* can also cause pulmonary TB (air borne infection) in patients, who live in contactto cattle, particularly in rural areas. Transmission of TB due to *M. bovis* or *M .tuberculosis* from HTB patients to cattle is also possible mainly due to contamination of pasture from urogenital TB cases in man (O'Reilly and Daborn., 1995). Ethiopia is a country where the impact of BTB is particularly important and it is one of the 13th country singled out by (WHO, 1997) as a home for 75% of the world's TB cases. TB is one of the top three in Africa by the number of TB patients (Dye *et al*., 1999). However, there are no records of nationwide distribution because of inadequate disease surveillance and lack of good diagnostic facilities (Ameni and Roger, 1998; Ameni*et al*., 2001). BTB is considered endemic in Ethiopia based on abattoir inspection (Asseged *et al*., 2004; Girmay*et al*.,2012) and tuberculin test survey (Asseged*et al*., 2000).The present communication describes the growing significance of *M.bovis* in human health

Etiology

Mycobacteriun bovis is an acid fast, aerobic, non-motile, non-spore-forming, slow growing, facultative intracellular pathogen which can survive and multiply inside the macrophages and other mammalian cells (Pal, 2007). It belongs to the genus *Mycobacterium* of the family *Mycobcateriacae*. The phylogenetic analysis of the genome pathogenic *Mycobacterium* has shown that are except *M. avium*,they belong to a single genetic species: *Mycobacterium tuberculosis*

complex. *M. bovis* belongs to the *M. tuberculosis* complex, which comprised of *M. tuberculosis*, *M. bovis* subspecies *caprae* (Pal and Boru, 2012).

Epidemiology of *M. bovis*

Source of infection and mode of transmission

Cattle serve as the principal reservoir of *M. bovis*. Humans can be infected with *M. bovis* where cattle are reared for milk production (Girmay*et al*., 2012). Organisms are excreted in the exhaled air, nasal discharge, milk, urine, vaginal and uterine discharges and discharges from open peripheral lymph nodes. Animals with gross lesions that communicate with airways, skin or intestinal lumen are obvious disseminators of infection. In the early stages of the disease before any lesions are visible, cattle may also exert viable *mycobacterium* in nasal and tracheal mucus. In experimentally infected cattle excretion of the organism commences about 90 days after infection (Radostits*et al*., 2000).Inter-human transmission of *M. bovis* is possible, but few cases have been confirmed (Acha and Szyfres, 2001).

Risk Factors conductive to the spreading of **M. bovis** *infection in humans*

Occupation

Professional occupation involving workers such as abattoir personnel, veterinarians and laboratory technicians, animals' caretaker in zoos and those who are working in animal reservations and at national parks can also acquire the infection in due course of their regular work (Shitaye*et al*., 2007).

Cultures and Traditions

In developing countries, particularly in Africa, patients'beliefs and cultural traditions are major obstacles to implement the designed tuberculosis control strategies. TB is stigmatized in many cultures and traditions, and it remains as powerful as that of HIV/ADIS, which further complicates the process of investigation by patients hiding their TB status due to discriminatory view about tuberculosis patients. Patients claimed to be unaware of the need to take a full course of treatment, and that the red color of the urine due to rifampicin treatment adversely affected their partners, resulting in sexual abstention during treatment (Ayele *et al*., 2004).The traditional feeding habits of consuming raw animal products in high proportion of the society of developing countries particularly in pastoralist community assumed to be major risk factors in acquiring *Mycobacterium* infection from animal origin (Pal, 2012). In addition to the consumption of raw milk, in some parts of developing countries due to cultural reasons, there is a habit of consuming certain raw visceral organs immediately after slaughter. This in turn may increase the chance of acquiring *M. bovis* infection. Also, during drought seasons when milk production from cow is not sufficient to provide for need of the family, pastoralist in some African country *e.g.,*Maasai people in Tanzania draw blood from the jugular vein of their animal and drink fresh or mixed with milk. Fresh blood is also given to ill person and to women after they have given birth (Dabron *et al*., 1996). Close physical contact between human and potentially infected animals is not uncommon in under developed countries. In most cases, cattle and humans in developing countries shares the same house. This, of course, increases the chance of contracting diseases such as BTB from cattle to human beings and vice versa (Cosivi*et al*,. 1998).

Immunosuppressive Disease including HIV infection

In many developing countries, it is very likely that cattle-to-human transmission of *M. bovis* regularly occurs. May be in few cases such transmissions may lead to self-limiting lesions, and possibly, induction of protective immunity against further infection. However, protective immunity suppressed by HIV infection and other immunosuppressive conditions, would result reactivation of tuberculosis leading to overt and progressive disease (Scanga et al., 1999). Thus, in regions with a high prevalence of HIV infection, a cycle of cattle-to-human, human- to-human and human- to- cattle transmission of disease could be established (Grange *et al.*, 1994).

Illiteracy

It is pertinent to mention that health education should be imparted to the public about the source of infection, mode of transmission, severity of the disease, personal hygiene and preventive measures (Pal, 2007). However, like in most African countries, in Ethiopia,

illiteracy is yet another unsolved problem in most rural communities in particular inability to read, write. In addition, other risk factors include lack of common knowledge among the rural people on epidemiology of various diseases including *M. bovis* infection and lack of effective prevention and control programmes (Shitaye*et al*., 2007).

Lack of reference laboratory

The relatively low isolation rate of *M. bovis* from HTB cases in developing countries could be partly explained by the extensive use of microscopy for confirmation of suspected cases of TB. This technique does not permit differentiation between species of mycobacterium, but the gold standard differentiation of species is based on culture methods supported with biochemical test and molecular technique. The absence of reference laboratory results in under estimation of zoonotic TB in human being (Cosivi*et al*., 1995).

Geographic distribution

Although bovine tuberculosis was once found worldwide, control programmes have eliminated or nearly eliminated this disease from domesticated animals in many countries. However, wild animals, which act as important reservoir of tubercle bacilli, may pose a serious threat in control and eradication programmes (Pal and Boru, 2012). 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, Bar-bados and Israel. Eradication programmes are in progress in other European countries (Raghvendra et al., 2010). Although bovine tuberculosis has been eradicated from the majority of U.S. states, a few infected herds continue to be reported. From 2002 to 2013, bovine tuberculosis has been detected on numerous dairies in California (McCluskey et al., 2014), and over the period of time, a few US states may periodically lose their disease-free status. Bovine tuberculosis is still widespread in Africa, parts of Asia and some Middle East countries (Corner, 2006).Figure 1 represents WHO report showing the estimated global incidence rate of TB in 2011.
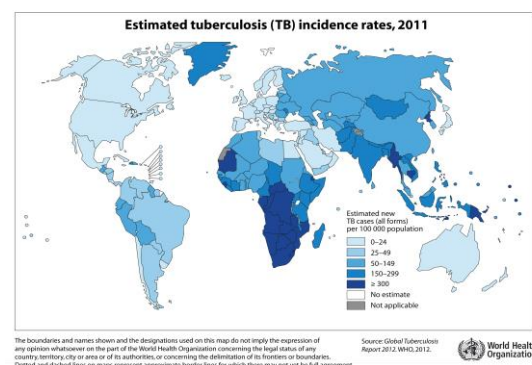

Figure 1. The WHO estimated global incidence rate of TB in 2011.

Pathogenesis

M. bovis enters the host though respiratory, alimentary, cutaneous genital routes. It may be self-limiting to fulminating disease with extensive tissue destruction. Miliary tuberculosis is the most severe form of disease with haematogenous spreading as a result of lysis of phagosomin to the macrophages. This releases bacteria into the blood from the primary foci and secondary seeding to various tissues (Anderson, 1997).

Bacilli are engulfed by alveolar macrophages in the circulation and then become established in the lymph nodes. The cellular response attempt to control the pathogen results in an accumulation of large number of phagocytes, which leads to the formation of macroscopic lesion or a tubercle. Cell mediated immunity (CMI) emerges 10-12 days after infection, triggers the release of cytokines from T-lymphocytes. This activates the bacteriostatic effect of the macrophages and accelerates the recruitment of additional blood borne mononuclear cell into the site resulting in delayed type of hypersensitivity reaction. Necrosis results from the delayed type hypersensitivity reaction. The gross appearance of tubercle is usually firm yellow rarely a yellowish caseous necrotic material or calcified tissue is observed (Quinn *et al*, 2002).

Public health impact of *M. bovis*

***Global situation and trend of human tuberculosis caused by* M. bovis.**

The actual incidence of TB across the globe is greatly underestimated. In 1995, WHO reported 3.3 million cases of TB whereas a more likely number is 8.8 million. Among the cases about 62% occurred in the Southeast Asian and Western Pacific regions, 16% in Sub-Saharan Africa, and 7% to 8% in each of the regions of the American, Eastern Mediterranean, and Europe. In continents, such as Africa, Asia, and South America (Caribbean countries), the prevalence of the disease was recorded at 46%; 44%; and 35%, respectively. However, on the other hand, in industrialized nations, human TB due to *M. bovis* is relatively rare as result of proper milk pasteurization and animal TB control programme (Grange, 2001; Pal and Boru, 2012).

In 1990-1999, in the absence of effective control, global TB incidence and deaths were reached 88 million and 30 million, respectively (Dolin *et al.,* 1994). Because of the HIV epidemic, the incidence rate of TB has been increased in Sub-Saharan Africa in the last decade and the total number of new cases doubled by the year 2000. Due to immigration particularly from countries with a high prevalence of dual HIV and TB infection, in industrialized countries, a slight increase in the incidence rate and total cases of TB has been observed in last few years (Davies PD, 2003). In 2000, approximately 40% of these HIV-attributable cases were occurring in Sub-Saharan Africa and 40% in Southeast Asia. *M. tuberculosis* will be largely responsible for the new TB cases and deaths, but an unknown, and potentially important, proportion will be caused by *M. bovis* (Cosivi *et al.,* 1995).

M. bovis and the pulmonary tuberculosis

Pulmonary tuberculosis (TB) is common worldwide infection and medical and social problem causing high mortality and morbidity, perhaps especially in developing countries. In developing countries because of close physical contact between human and animals and potentially infected animals airborne transmission of *M. bovis* is occurs. In many African countries, cattle are an integral part of human social life, represent wealth and gathering them in the same house with human is common. It has been reported in Nigeria that from sputum samples of 102 *M. tuberculosis* complex isolate, 4 (3.9%) were *M. bovis* (Idigbe *et al.,* 1986).

In addition, developing countries working in agriculture, a significant proportion of them are at risk for bovine tuberculosis. Researched in Australia earlier suggested that TB should be considered as occupational hazard in abettor and meat industries because the disease could be transmitted to human through inhalation (Robinson *et al.,* 1989). However, the situation may not be the same now there.

M. bovis as a cause of extrapulmonary tuberculosis

The most prevalent form of TB caused by *M. bovis* in man is extrapulmonary- a disseminated infection outside the lungs commonly involving lymphnodes, pleura, osteoarticular junctions and other areas (Figure 2). This is not because of affinity, but that is most commonly transmitted by consumption of raw milk products (Kleeberg, 1994). The mycobacterium may spread through lymphatic or haematogenous dissemination to any tract or through coughing and swallowing to the gastrointestinal tract. Bacteria may remain dormant for years at a particular site before causing disease. Since extrapulmonary TB affects virtually all organs, it has a wide variety of clinical manifestations, which causes difficulty and delay in diagnosis obtaining material for culture confirmation of extrapulmonary TB is much more difficult than obtaining material for culture confirmation of pulmonary TB. Extra pulmonary TB is more often diagnosed in women and young patients (Gonzalez *et al.,* 2003).

This form of TB occurs more commonly in immunosuppressed persons and children. In those with HIV, this occurs in more than 50% of cases. Notable extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott's disease of the spine), among others. When it spreads to the bones, it is also known as "osseous tuberculosis". A form of osteomyelitis sometimes bursting of a tubercular abscess through skin results in tuberculous ulcer. An ulcer originating from nearby infected lymph nodes are painless, slowly enlarging and has

an appearance of "wash leather". A potentially more serious, wide spread form of TB is called "disseminated" TB, commonly known as miliary tuberculosis. Miliary TB makes up about 10% of extrapulmonary cases (Jindal, 2011).The most common form of extrapulmonary tuberculosis is lymphadenitis tuberculosis with multiple differential diagnosis. Demonstration of the etiological agent by smear microscopy or culture FNA specimens is often unsuccessful. Fine needle aspirate specimens from 40 patients presenting a rural health center in south Ethiopia and diagnosed as positive for TBLN on the basis of clinical and cytological criteria were analyzed to mycobacterial DNA by PCR. Thirty (75%) had cervical lymphadenitis and 11 (27.5%) were seropostive for human immunodeficiency virus (HIV) (Kidane *et al.,* 2002).
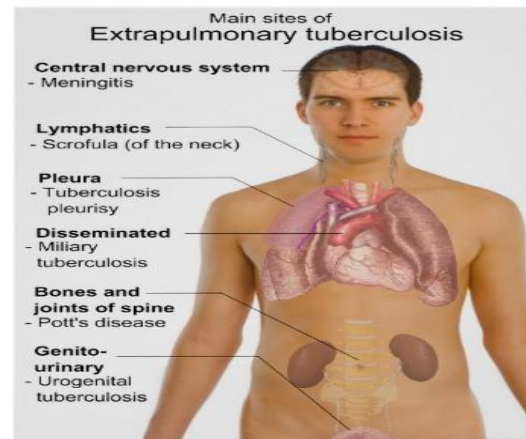

Figure 2: Main sites of Extrapulmonary tuberculosis (Hemal, 2001).

Diagnosis of human Tuberculosis

Bacteriology

The presence of acid-fast-bacilli (AFB) on a sputum smear or other specimen often indicates TB disease. Acid-fast microscopy is easy and quick, but it does not confirm a diagnosis of TB because some acid-fast-bacilli are not tuberculosis. Therefore, a culture is done on all initial samples to confirm the diagnosis. (However, a positive culture is not always necessary to begin or continue treatment for TB.) A positive culture for tuberculosis confirms the diagnosis of TB disease. Culture examinations should be completed on all specimens, regardless of AFB smear results (Harrison *et al.,* 1994).

Serology

It has rapid diagnostic value based on the recognition of IgG antibody to selected Mycobacterium antigen and the use enzyme linked immunosorbent assay (ELISA) techniques have been and appear to offer promise, with sensitivity similar to that of sputum microscopy (less sensitive). In addition, there are few more serological test such as Brock TB Stat-Pak testing (Chambers *et al.,* 2010), Animal-Side Antibody Assays (Lyashchenko *et al.,* 2011) and monoclonal antibody (TB72) based serological test (Ivanyi *et al.,* 1983) for detection on TB in human and animal. Serology may have its great application in case where sputum is not available and in case of extrapulmonary tuberculosis (Harrison *et al.,* 1994).

Polymerase chain reaction (PCR)

One of the most reliable and accurate molecular method that target the detection of genes (nucleic acid) specific for a microorganism is Polymerase Chain Reaction (PCR). This nucleic acid amplification technique tests represent a major advance in the diagnosis of TB because of its high sensitivity and specificity. PCR allows amplification of genes (nucleic acid sequences) that are unique to *Mycobacterium* species and could be detected directly from clinical specimens. Among the genes that are commonly used for the detection of *Mycobacterium* are 16S rRNA genes, *mmpS6* gene, *pnc*A gene, *hupB* gene, antigen genes *e.g., mpb70* and *mpb64* and the insertion sequence IS6110, IS1081 (Gormley*et al.,* 1999; Broccolo *et al.,* 2003; Young *et al.,* 2005), IS900PCR (Sukumar *et al.,* 2014). The method also offer better accuracy than AFB staining and requires very less time than cultural technique (Eisench *et al.,* 1991). Several types PCR assays such as conventional end point analysis based PCR, multiplex-PCR and real-time PCR are available for the detection of TB. One of the major advantages of PCR is its detection

limit, since it can detect as few as 5 to ten AFB bacilli present in clinical samples (Singh and Seth, 2002).

Bronchoscopy

A bronchoscopy is a medical procedure that allows visualization of the inside of a person's airways .The airways is called the bronchial tubes or bronchi. Bronchoscopy might be needed for specimen collection, especially if previous results have been non diagnostic and doubt exists as to the diagnosis. At other times, bronchoscopy is considered because TB is among several other diagnoses being considered. If possible, examine three spontaneous or induced sputum to exclude a diagnosis of TB disease before bronchoscopy. If possible, avoid bronchoscopy on patients with suspected or confirmed TB disease or postpone the procedure until the patient is determined to be non-infectious, by confirmation of the three negative AFB sputum smear results. Bronchial washings, brushings, and biopsy specimens may be obtained, depending on the bronchoscopy findings. Sputum collected after a bronchoscopy may also be useful for a diagnosis. A bronchoscopy should never be substituted for sputum collection, but rather used as an additional diagnostic procedure (CDC, 2005).

Radiology

A posterior-anterior chest radiograph has used to detect chest abnormalities and evaluation of tuberculosis. Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation. These abnormalities may suggest TB, but cannot be used to definitively diagnose TB. However, a chest radiograph may be used to rule out the possibility of pulmonary TB in a person who has had a positive reaction to a TST or TB blood test and no symptoms of disease (Harrison *et al*., 1994).

Tuberculin test

Most people infected with TB have no sign of the disease as the bacterium is 'sleeping' or dormant. This is called latent TB. Some people with latent TB will develop TB disease or active TB. TB disease can affect any part of the body but usually affects the lungs. The tuberculin skin test (TST) is also known as the Mantoux test. It is a skin test to detect if you have been infected with TB bacteria. It done to detect latent TB infection in a person who may have been exposed to someone diagnosed with active TB, to obtain a baseline before employment in a health care facility or travel to a high TB risk region, and before BCG vaccination. A small amount of purified protein derived (PPD) from dead TB bacteria is injected under the top layer of the skin on the forearm using a sterile disposable needle and syringe. Please see Yang *et al.,* (2012) for details on PPD. A small blister will appear at the site, and will disappear within 20minutes. There may be a small amount of blood at the needle site. One should return to the clinic 3 days later to have the site assessed for any reaction. The reaction or lump is measured in millimeters. Tuberculin test is standard ante mortem test in cattle and is based on delayed type hypersensitivity. Slants of Lowenstein-Jensen medium without glycerol and with 0.4% sodium pyruvate inoculated with centrifuged deposit and incubated aerobically at 37oc for up to 8 weeks (Pal and Boru, 2012).

Prevention and control of *M. bovis* infection

Therapy

The overall goals for treatment of tuberculosis are 1) to cure the individual patient, and 2) to minimize the transmission of tuberculosis to other persons. Thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides. For this reason the prescribing physician, be he/she in the public or private sector, is carrying out public health function with responsibility not only for prescribing an appropriate regimen but also for successful completion of therapy. Prescribing physician responsibility for treatment completion is a fundamental principle in tuberculosis control. However, given a clear understanding of roles and responsibilities, oversight of treatment may be shared between a public health program and a private physician. It is strongly recommended that patient-centered care be the initial management strategy, regardless of the source of supervision. This strategy should always include an adherence plan that emphasizes directly observed therapy (DOT), in which patients are observed to ingest each dose of anti tuberculosis medications, to maximize the likelihood of completion of therapy. Programs utilizing DOT as the central element in a comprehensive, patient-centered approach to case management (enhanced DOT) have higher rates of treatment completion than less intensive strategies. Each patient's management

plan should be individualized to incorporate measures that facilitate adherence to the drug regimen Such measures may include, for example, social service support, treatment incentives and enablers, housing assistance, referral for treatment of substance abuse, and coordination of tuberculosis services with those of other providers (CDC, 2003). Chemotherapy is entirely impractical in animals because of the high cost of treatment, the frequent recurrence of the diseases when the treatment is stopped and the possibility of the development of multidrug resistant strain of *M. bovis* (O'Reilly and Daborn, 1995).

Sanitary prophylaxis

In many developing countries, a test and slaughter program would be inappropriate because of lack of resources, political instability or social unacceptability of the control methods and the presence of reservoir hosts. But there are alternative strategies like programmes based on slaughter house surveillance, trace back of tuberculoses animals to herd of origin, test and isolation of animals, housing of animals separately from animals. Measures like trailing public health personnel, public education, proper hygiene practice, maintaining and reinforcing the policy of boiling or pasteurization of milk and dairy products, as well as protecting workers in animals related occupations especially animal attendants and meat industry workers need to be taken (WHO, 2004). Removal of calves at birth and feeding on either the milk of sound cows or pasteurized milk reduces the risk of infection significantly from cattle to other animals and infection of man can be avoid by pasteurization of milk (Cosivi *et al*., 1998;Pal,2007).

Vaccination

The vaccine that is used for the control of TB is BCG (Bacillus Calmette-Guerin). It is the only vaccine available currently for use against tuberculosis in humans (da Costa *et al.,* 2014). It is a live attenuated strain of *M. bovis* that is not able to cause disease but induce immunity. The original strain was developed at the Pasteur Institute in Paris between 1908 and 1921 through the repeated passage by Albert Calmette and his assistant/colleague Camille Guérin. The Pasteur strain of BCG serves as the reference strain of the vaccine, and its complete genome sequence has been determined (Borsch *et al*., 2007). Subsequent strains have undergone further development through repeated sub culturing in many laboratories around the world. These strains are now known to differ in terms of their genome and a number of biologically intriguing phenotypes, such as those with the ability to make virulence lipids and produce antigens (Behr *et al*., 2000). The genealogy of BCG strain is presented in Figure 3.
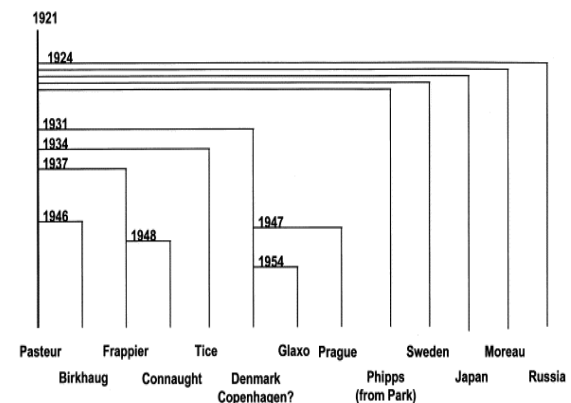
Figure 3.Genealogy of BCG strain dissemination. Vertical axis scales to time. Horizontal dimension does not scale to genetic difference (Behr and Small, 1999)

BCG is given to infants as a part of the immunization program recommended by the World Health Organization (WHO) in TB endemic area. In adults, the effectiveness of BCG has varied widely in large-scale studies. Patient vaccinated with BCG gives positive skin test (tuberculin) thus limiting the effectiveness of the PPD skin test to identify new infections. BCG is not recommended for general use in many countries of the world, particularly where the disease is not present or endemic.

Although BCG can be effective in reducing the incidence of childhood tuberculosis, particularly meningitis, it is relatively ineffective in protecting against adult tuberculosis, and does not prevent infection with the organism. Thus, BCG immunized still

become infected with *M. tuberculosis*, can develop active tuberculosis, and can harbor the organism and reactivate later in life. It is also important to note that the BCG vaccination should not be given to woman during pregnancy and persons who are immunosuppressed particularly to the HIV positive patient. In addition to BCG, research is going on for the development of other vaccine to control TB including recombinant BCG. Among them vaccine VPM1002, also called rBCGΔureC:hly, is currently in human clinical trials, however, much work need to done to make it effective (da Costa *et al.,* 2014).

For cattle, in infected countries where there is no test and slaughter control scheme, BCG vaccination may be used to reduce the spread of infection in cattle, but probably will not be effective, since the vaccine does not work satisfactorily in animal (Buddle BM, 2001). The use of the test and slaughter policy to control bovine TB is economically and socially unacceptable in developing countries (OIE, 2004).

Conclusions

Mycobacterium bovis is the principal agent responsible for tuberculosis in domestic and wild mammals, but also infects humans, causing zoonotic tuberculosis. The transmission route from animals to humans and vice versa is well known and the application of fingerprinting tools facilitates analysis of the molecular epidemiology of *M. bovis* in animal-to-human and human-to-human transmission (Pérez-Lago *et al.,* 2013). Although the epidemiology of bovine tuberculosis is well-understood and effective control in elimination strategies have been known for long time, the disease is still widely distributed and neglected in most developing counties. The frequent report of human cases of lymphadenitis TB from different health centers across the country may indicate the zoonotic importance of the disease. HIV infection is the leading risk factor for tuberculosis because it promotes the progression of latent or recent infection of mycobacterium to active disease and also increases the rate of occurrence of TB. The strict meat inspection, regular tuberculin testing, proper pasteurization of milk, thorough cooking of meat, early diagnosis and prompt treatment and health education of the public will certainly help to reduce the prevalence and incidence of tuberculosis which is an international health problem.Since the disease infects both the human and animal 'One health' approach focusing strong collaboration between veterinary and human health care researchers are crucial for the prevention and control of the disease (Pérez-Lago *et al.,* 2013). Still there are areas that need to be addressed that includes strong TB surveillance systemin rural and remote areas, vaccination of mobile populations (both animal and human) and improved public awareness for the prevention and control of TB in some part of the world particularly in Sub-Saharan African (Grater *et al.,* 2014).

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