Chapter 2

Zoonotic Tuberculosis: A Concern and Strategies to Combat

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Abstract

Mycobacterium bovis is the main causal agent of bovine tuberculosis that causes zoonotic tuberculosis in humans. The most common routes of transmission of the agent to human are airborne transmission, consumption of unpasteurized milk, direct contact with infected animals or untreated animal products. Conventional diagnostic methods in combination with modern molecular and immunological techniques should be used for early and accurate diagnosis of the disease. Some of the challenges to tackle and eradicate zoonotic TB in developing countries are having many hosts, absence of early diagnosis, presence of other acute diseases, being economically unable to implement control strategies, and other social and cultural issues. Usually treatment is not recommended in animals but vaccination is carried out in some countries as a preventive measure. Due to the grave consequences of *M. bovis* infection on animal and human health, it is necessary to introduce accurate control measures to reduce the risk of disease in human and animal populations. Proper food hygiene practices, slaughter of the affected animals in developed countries, and segregation of the suspected animals in developing countries along with stronger intersectoral collaboration between the veterinary and medical professions are important for the control of the disease.

Keywords: *M. bovis*, zoonoses, developing countries, challenges, one health

1. Introduction

Livestock plays an important role in the lives of people throughout the world. They provide dietary protein through meat and milk, materials like wool and leather, and draught power for

agricultural activities and contribute to the livelihoods of around 70% of the world's population living in poverty. Livestock is central to survival strategies of poor families, can serve as a repository of a family's wealth, and may be sold as an emergency source of cash, in some settings; their ownership is linked to social status or may also be important for ceremonial, cultural, and religious significance. Due to unavoidable interaction of man and animals; zoonotic diseases remain a genuine threat to public health. Zoonotic diseases are the diseases or infections which are naturally transmitted between animals and humans, for example, tuberculosis, brucellosis, leptospirosis, and so on. In most cases, animals play an essential role in maintaining, distributing, and actually transmitting the infection up to varying degrees into the nature. One of the economically significant zoonotic diseases worldwide is bovine tuberculosis (TB) because of serious public health consequences, high cost of eradication programs mainly in developing countries, and trade restriction on animals and their products [1–4]. It is said to be the leading cause of death by infectious diseases [5]. World Health Organization (WHO) classified bovine tuberculosis among seven neglected zoonotic diseases having the potential to infect man [6].

M. bovis mainly affects cattle, which are the most important animal reservoirs and can be established in wildlife. The link between animal and human tuberculosis has long always been known to be strong, as shown by the works of Villemin [7] and Koch [8], which demonstrated the cross-adaptability of the tubercle bacilli from one species to another and pointed out the danger that tuberculosis could be transmitted from animals to humans [7]. The infection currently poses a major concern in human populations in developing countries, as humans and animals share the same microenvironment. It has been estimated that zoonotic transmission of *M. bovis* is responsible for 10–15% of new human TB cases in developing countries [9]. Bovine TB has been largely eradicated from herds in the developed world by animal TB control and elimination programs, that is, test-and-slaughter programs have drastically reduced the incidence of disease in both animals and humans [10, 11]. However, in developing countries, animal TB is widely distributed and control measures are not applied or are applied sporadically [12, 13].

The human burden of disease cannot be reduced without improving the standards of food safety and controlling bovine TB in the animal reservoir. As with other zoonotic diseases, zoonotic TB cannot be controlled by the human health sector alone. Animal health and food safety sectors must be engaged to address the role of animals in maintaining and transmitting *M. bovis*. The present review highlights chronic multi-species zoonotic TB, its diagnosis prevention and control, veterinary public health challenges, and strategies to combat this important disease.

2. Epidemiology

2.1. The etiological agent

Mycobacteria belong to the order Actinomycetales, family Mycobacteriaceae. The genus *Mycobacterium* includes *Mycobacterium tuberculosis* and *Mycobacterium avium* complexes, other pathogenic *Mycobacteria*, and numerous species of saprophytic microorganisms present in soil and water. The etiologic agents of mammalian tuberculosis are *Mycobacterium tuberculosis*, the main cause of human tuberculosis; *M. bovis*, the agent of bovine tuberculosis; and *M. africanum*,

which causes human tuberculosis in tropical Africa. This last species has characteristics halfway between those of *M. tuberculosis* and *M. bovis*. *M. bovis* is the principal agent of zoonotic tuberculosis. The distribution of *M. bovis* and *M. tuberculosis* is worldwide. *M. africanum* is prevalent in Africa, but it has also been isolated in Germany and England. *M. africanum* strains phenotypically related to *M. tuberculosis* are nitrase positive and are found in Western Africa while those which are similar to *M. bovis* are nitrase negative and are isolated more frequently in Eastern Africa.

The genus mycobacterium is phenotypically characterized as a facultative intracellular microbe, non-capsular, non-spore forming, non-motile, obligate aerobic, and thin-rod bacteria, usually straight or slightly curved having a length of 1–10 length and width of 0.2–0.6 μm. Its cell wall is rich in lipids, that is, mycolic acid, a thick waxy coat responsible for acid fastness, hydrophobicity, greatly contributing to bacterium resistance to many disinfectants, common laboratory stains, antibiotics, and physical injuries [14, 15].

M. bovis is a member of the mycobacterium tuberculosis complex (MTC) and based on 16S ribosomal RNA sequence studies it shared more than 99.95% of identity with other members of MTC [3, 16]. The MTC includes five mycobacterium species, *M. tuberculosis*, *M. canettii*, *M. africanum*, *M. microti*, *M. bovis*, and two subspecies—*M. caprae* and *M. pinnipedii* [17]. In the environment *M. bovis* can survive for various months especially in cold, dark, and moist conditions. The survival period varies from 18 to 332 days at 12–24°C which is dependent on sunlight exposure. It is found that *M. bovis* best survives in frozen tissue and there are adverse effects of tissue preservatives, that is, sodium tetraborate on viability [18]. It has been found that the culture of the organism can be done for approximately 2 years in samples that are stored artificially [14, 18].

2.2. Host range

The most important causes of bovine TB in cattle are *M. bovis* and *M. caprae*, both of which cause infectious diseases [19–22]. *M. bovis* has one of the broadest host ranges of all known pathogens and has been diagnosed worldwide. Cattle are considered to be the true hosts of *M. bovis* [23]. However the isolations of *M. bovis* has also been detected from domestic animals like buffaloes, sheep, goats, pigs, equines, camels, and so on, along with other animals like deer, antelopes, bison, wild boars, primates, llamas, kudus, elephants, foxes, mink, ferrets, rats, elands, tapirs, elks, sitatungas, oryxes, addaxes, rhinoceroses, possums, ground squirrels, badgers, otters, seals, hares, moles, raccoons, coyotes and lions, tigers, leopards, and lynx [23, 24]. The natural movement of these reservoir animals increases the spread of the disease to domestic animals [25]. *M. caprae* has been reported in many European countries such as Austria, France, Germany, Hungary, Italy, Slovenia, and the Czech Republic. A disease caused by *M. caprae* is not substantially different from that caused by *M. bovis* and the same tests can be used for its diagnosis [26].

2.3. Transmission

Transmission of *M. bovis* can occur between animals, from animals to humans, and vice versa and rarely in between humans [27]. The transmission of *M. bovis* between animals occurs mainly through aerosols. Transmission through other routes like cutaneous, congenital, and genital routes has also been reported. Close contact among animals and intensive breeding

increase the rate of transmission [28]. Other factors like long survival periods of the organism in the environment also contribute to an increased risk of infection [29, 30]. Suckling calves can get the infection through consumption of infected milk. The infected bull semen may transmit diseases through artificial insemination [18].

Humans acquire the *M. bovis* infection from cattle directly by erogenous route or through the direct contact with material contaminated with the secretions of an infected animal or the herd [31, 32]. The individuals at risk are farm workers, zookeepers, milkers, animal dealers, veterinarians, abattoir workers, meat inspectors, autopsy personnel, laboratory personnel, and owners of potential tuberculous pets [33–35]. People in these occupations may develop pulmonary tuberculosis from *M. bovis* and in turn put other humans and susceptible animals at risk [36, 37]. Indirectly, man acquires the disease from animal sources by consumption of unpasteurized infected milk and ingestion of meat and meat products from slaughtered infected cattle [13, 38–41]. Therefore tuberculosis can be foodborne also [42]. The consumption of contaminated milk products possesses more risks than infected meat products because badly infected carcasses are mostly condemned and meat is generally thoroughly cooked [43]. People suffering from *M. bovis* tuberculosis can retransmit the infection to cattle; however, this is not common [44].

2.4. Geographic distribution

Zoonotic TB is distributed globally and is more prevalent in most of Africa, parts of Asia and of the Americas except Antarctica, Caribbean islands, parts of South America and Australia, Iceland, Denmark, Sweden, Norway, Finland, Austria, Switzerland, Luxembourg, Latvia, Slovakia, Lithuania, Estonia, the Czech Republic, Canada, Singapore, Jamaica, Barbados, and Israel [45]. Although most of the developed countries have reduced or eliminated bovine TB from their cattle population, however, the disease is still present in the wildlife of United Kingdom, Canada, the United States, and New Zealand [23]. Eradication programs are in progress in other European countries, Japan, New Zealand, the United States, Mexico, and some countries of Central and South America where it has been eradicated by following strict test-and-slaughter policies [46].

3. Clinical presentation

3.1. In animals

Bovine TB is a chronic debilitating disease usually characterized by formation of nodular granulomas known as tubercles. In many animals the course of the infection is chronic and signs may be absent, even in advanced cases when many organs may be involved. Subclinical signs include weakness, dyspnea, anorexia, emaciation, enlargement of lymph nodes, and cough, particularly with advanced tuberculosis. Lesions are commonly observed in the lymph nodes mainly of the head and thorax, lungs, intestines, liver, spleen, pleura, and peritoneum. Head and neck lymph nodes may become visibly affected, sometimes rupture, drain, and in advanced cases may be greatly enlarged and may obstruct air passages, alimentary tract, or

blood vessels. Clinical signs vary with the involvement of the lung manifested through cough, dyspnea, and other signs of low-grade pneumonia which can be induced by changes in temperature or manual pressure on the trachea. Digestive tract involvement is manifested by intermittent diarrhea or constipation, extreme emaciation, and acute respiratory distress may occur during the terminal stages of tuberculosis [26].

3.2. In humans

M. bovis infection in humans has similar clinical forms as those caused by *M. tuberculosis* [27, 34, 44]. Most of the studies have suggested that the common clinical manifestation of *M. bovis* infection in man is associated with the extra-pulmonary form of the disease; however, about half of the post-primary cases involve the lung which is responsible for human-to-human transmission of tuberculosis due to *M. bovis* [13, 31, 44, 47]. The primary infection of the organism in the intestine may heal or it may progress in the intestines or disseminate to other organs [48]. Cervical lymphadenopathy, intestinal lesions, chronic skin tuberculosis, and other non-pulmonary forms are particularly common [13]. Infection due to *M bovis* in humans usually has a prolonged course and symptoms generally takes months or years to appear. Sometimes, the bacteria remain dormant in the host without causing diseases [23]. The common clinical signs of zoonotic TB include loss of appetite, diarrhea, weight loss, intermittent fever, intermittent hacking cough, large prominent lymph nodes, weakness, and so on.

Young children infected with *M. bovis* typically have abdominal infections and older patients suffer from swollen and sometimes ulcerated lymph glands in the neck [49]. Pulmonary disease is more common in people with reactivated infections [50] and this would occur only when some of the animals had active tuberculosis [32]. The symptoms may include fever, cough, chest pain, cavitation, and hemoptysis [50]. The pulmonary form of tuberculosis occurs less frequently and is usually occupationally related [44].

4. Zoonotic TB: a concern

Bovine TB affects the national and international economy in different ways. It is extremely difficult to determine the economic impact of bovine TB on livestock production. The presence of bovine TB infection in livestock reduces the livestock productivity and economically devastates the cattle industry especially the dairy sector. Some losses are related to the animal production, marketing, or trading of the animals as well as the cost involvement while implementing surveillance and control programs. These losses are also extremely important when endangered wildlife species get involved [51, 52]. The direct productivity losses due to bovine TB can be categorized into "on-farm" losses and losses after the slaughtering of animals. On-farm losses consist of the losses from decreased milk and meat production, the increased reproduction efforts, and replacement costs for infected cattle while losses during slaughter consist of the cost of cattle condemnation and retention, with the loss from condemnation being essentially the purchased value of a slaughter animal and the loss [51]. Along with the direct productivity losses, bovine TB has profound economic consequences on international trade; it affects access to foreign markets due to import bans on animals and animal products

from countries where the disease is enzootic. The presence of the disease in wildlife is not only difficult to eradicate and costly but also bovine TB can theoretically affect entire ecosystems with unpredictable impacts in many areas of private interest, for example, tourism [51].

In 2016, WHO estimated 147,000 new human cases of zoonotic TB in people and around 12,500 deaths due to the disease. The implications of zoonotic TB extend beyond human health. Bovine TB threatens the well-being of communities that rely on livestock for their livelihoods. The African region carries the heaviest burden of disease and death due to zoonotic TB, followed by the Southeast Asian region. However, cases of zoonotic TB in people are uncommon in countries where bovine TB in cattle is controlled and where standards of food safety are high. The true burden of zoonotic TB is likely to be underestimated due to a lack of routine surveillance data from most countries. Therefore, the number of people affected by zoonotic TB annually, and thus suffering from health challenges caused by *M. bovis* infection, might be higher than currently estimated in particular, countries where bovine TB is endemic and where laboratory capacity is limited [60].

Current diagnostics for human TB are focused on pulmonary diseases associated with *M. tuberculosis* (sputum smears examination) but zoonotic tuberculosis in human beings is frequently associated with extra-pulmonary tuberculosis and therefore initiation of treatment can be delayed [53, 54]. There is lack of testing to identify the *Mycobacterium* spp.; very few extra-pulmonary lesions are being tested, and requirements for mycobacterial culture for diagnostics are often skipped which contribute to under-reporting of human bovine TB cases [55–58]. Determination of species can add important information needed by epidemiological studies to identify sources of infection and routes of transmission [57, 59, 60].

A major challenge in the case of effective treatment and recovery of a patient infected with zoonotic TB is the natural resistance of *M. bovis* to pyrazinamide, one of the four essential medications used in the standard first-line anti-TB treatment regimen [61]. Most of the healthcare providers initiate the treatment without drug susceptibility testing due to which patients with zoonotic TB may receive inadequate treatment. This may lead to development of resistance to other anti-TB drugs. Resistance to additional drugs has also been reported in some *M. bovis* isolates, including rifampicin and isoniazid, and resistance to these two essential first-line drugs is defined as a multidrug-resistant TB, which is a major threat to human health globally. Such a shortcoming has significant implications for the treatment of zoonotic TB. Because most patients worldwide begin tuberculosis treatment without identification of the causative mycobacterium species, the risk of inadequate treatment of patients with undiagnosed *M. bovis* who do not have drug susceptibility testing is increased [62].

5. Diagnosis

Bovine tuberculosis in the live animal is usually diagnosed on the basis of the standard method for the detection of bovine tuberculosis, that is, delayed hypersensitivity reactions. It is done by injecting bovine tuberculin intradermally into the measured area, measuring subsequent swelling at the site of injection after 72 h and measuring skin thickness. Now, purified protein

derivative (PPD) products have been replaced by the heat-concentrated synthetic medium tuberculins due to their higher specificity and easier standardization. The identification of the pathogenic agent is done by the demonstration of acid-fast bacilli by microscopic examination. The *Mycobacterial* isolation on selective culture media and biochemical tests or DNA techniques, such as PCR, confirms infection. A gold standard for routine confirmation of infection is *Mycobacterial* culture method. Animal inoculation is rarely used because of animal welfare considerations. A number of blood tests are also been used for the identification of *M. bovis* [63]. These can be advantageous, especially with intractable cattle, zoo animals, and wildlife [64]. Blood-based laboratory tests now available are gamma-interferon assay, which uses an enzyme-linked immunosorbent assay (ELISA) as the detection method for interferon [65], the lymphocyte proliferation assay, which detects cell-mediated immune responses [66], and the indirect ELISA, which detects antibody responses.

Diagnosis of active TB in people in many parts of the world is based on the sputum smear examination or some rapid assays like Xpert MTB/RIF. But these commonly used tests are not able to differentiate the *M. tuberculosis* complex into the distinct species of *M. tuberculosis* and *M. bovis;* therefore, most cases of zoonotic TB are misclassified. The identification of *M. bovis* can be done by PCR and gene sequencing of culture isolates, but for these tests the proper collection of samples is very essential as zoonotic TB is extra-pulmonary. However, most of the countries lack the capacity to routinely conduct these tests.

6. Treatment

The treatment of animals with tuberculosis is not a favored option in eradication-conscious countries and is not economical. The Bacillus Calmette and Guérin (BCG) vaccine has advantages for use in cattle since the vaccine is safe, inexpensive, and is commercially produced for human application. However, the vaccination of animals with BCG is sensitive to the tuberculin skin test, and animals become test positive in the classical skin test at least for a significant period of post-vaccination. This is the reason why the test-and-slaughter-based control strategies based on tuberculin skin testing were favored above BCG vaccination in many countries [67].

In human tuberculosis, drugs like isoniazid, combinations of streptomycin and para-amino-salicylic, and other acids are commonly used. Long-term therapy requirement of the disease can create the chances of the development of multidrug-resistant (MDR), extremely drug resistant (XDR), and even totally drug resistant (TDR) bacterial strains if treatment regime is not properly followed. BCG vaccine is the only TB vaccine licensed for use in humans. BCG vaccine has variable levels of protection efficacy in humans against pulmonary TB in children and adults, ranging from 0–80% [68]. It is reported that the prevalence of MDR-TB in previously treated cases was 13.9% and in new cases only 2.3%, whereas the overall prevalence of MDR-TB was 5.7% in all cases [69]. Thus, previously treated cases were more vulnerable for being infected by the MDR-TB strain. Therefore, enhanced TB infection control activities, earliest case detection and treatment, strengthening and proper implementation of directly observed treatment, short course (DOTS), are suggested to reduce the burden of MDR-TB [69].

In human medicine, the treatment policy is based on second-line drug susceptibility testing. Most drug regimens currently used to treat MDR-TB include an aminoglycoside (e.g., streptomycin, kanamycin, amikacin) or capreomycin and a fluoroquinolone. The patients' MDR-TB should be managed by or in consultation with physicians experienced in the management of MDR-TB. The internationally recommended highly efficient and cost-effective strategy for TB control is DOTS (directly observed treatment short course). In this strategy, a healthcare worker at a healthcare center or family DOTS supporter at home gives the standard regimen to all MDR-TB confirmed cases daily under direct observation [70]. The regimens consist of the four drugs which are expected to be effective and the duration is a minimum of 18 months. Furthermore, continuous monitoring and capacity building for family DOTS supporters are essential components of the DOTS strategy. Effective treatments of drug susceptible to TB cure the patient, interrupt the TB transmission to other persons, and also prevent the development of drug-resistant strains.

7. Strategies to combat

The epidemiology of zoonotic TB varies throughout the world, depending on the human, livestock, and wildlife populations, and on existing TB control programs, environmental conditions, and the socio-economic status of countries or regions [71]. The relationship between humans, livestock, wildlife, and ecology in the epidemiology of zoonotic TB makes control of the diseases complex [72, 73]. Zoonotic TB is not a new disease but has long been neglected; burden of this disease in humans cannot be fully addressed without considering the animal reservoir and the risk of transmission at the animal-human interface. As with other zoonotic diseases, zoonotic TB cannot be controlled by the human or animal health sector alone. Human, animal health, and food safety sectors must be engaged to address the role of animals in maintaining and transmitting *M. bovis*. Therefore, "One Health" linking human, animal, and environmental health sector of World Health Organization (WHO), the Food and Agricultural Organization of the (FAO), and the World Organization for Animal Health (OIE) together with the International Union against Tuberculosis and Lung launched a comprehensive roadmap for zoonotic TB in people and bovine TB in animals in October 2017. The roadmap is on the basis of "One Health" approach and is centered under three core themes which consist of improvement of scientific evidence base, reduction in disease transmission at the animal-human interface, and strengthening the intersectoral collaboration.

An improvement in the scientific evidence base can be achieved by collecting, analyzing, and recording and a better quality data of the disease, by improving surveillance and reporting bovine TB in humans, livestock, and wildlife. For the better documentation and to generate accurate representative data which can differentiate *M. bovis* and *M. tuberculosis* infections, countries should strive to incorporate zoonotic TB into their routine surveillance activities. A better detection of cases requires health-care provider expertise and strengthened laboratories having improved access to accurate, rapid diagnostic tools coupled with reliable recording and reporting systems, that are case based and preferably electronic. Data regarding consequences of infectiousness, transmission, clinical presentation, and immunologic responses are important for

the development of a vaccine against all forms of TB. But improved surveillance and data quality will be unsuccessful without strengthened laboratory capacity and better access to appropriate diagnostic tools. Coordination and communication across the sectors is critical for investigating disease epidemiology at the human, livestock, and wildlife interface, including the relative importance of direct and indirect routes of transmission in different populations. Sharing the information within different sectors allows for the identification of patients in a particular geographical area which facilitates a target response for the prevention and control of the disease. To interpret multi-species data there is a need for new methodologies for describing multi-species transmission, such as modeling approaches incorporating genetic data. The biological differences in the host-pathogen interaction of *M. tuberculosis* versus *M. bovis* in humans should be further investigated.

Transmission of zoonotic TB at the animal-human interface can be reduced by developing strategies to improve animal health, identifying the pathways for risk and improving food safety. Healthier animal food supply depends on healthier animal population. For the disease-free state of the animal, both government and private veterinary services must be well organized and should be armed with the tools which can detect disease and reduce the disease prevalence. Developed countries can follow the test-and-slaughter programs by giving compensation to the farmers, post-mortem examinations of the carcass, and can trace-back the herds with appropriate tools to identify and implement control strategies. Similarly, in developing countries, a first step could be a target herd to be disease free in a particular zone of a country and this could gradually expand to other herds and zones. While doing this one must ensure the control of livestock movements from endemic areas to disease-free areas. The disease in a people can be prevented by reducing the risk of exposure and transmission of the infectious agent from animals to humans. Along with the knowledge of the principal routes of transmission some other factors such as sociocultural and economic factors should also be taken into the consideration. The use of modern technologies like sequencing, metagenomics, and phylogenetic analyses helps in characterization of sources of infection, mechanism of transmission, and investigation of drug resistance. Food safety practices can be improved by pasteurization of milk and sanitary inspection of carcasses at abattoirs which lead to removal the contaminated animal products from the food chain and also help in the tracing back animals to herds of origin.

Intersectoral collaboration can be achieved by adopting a "One Health" approach which suggests an intersectoral and multidisciplinary approach by engaging both public and private stakeholders. The most relevant sectors include human health sector, veterinary health sector, wildlife authorities, food safety authorities, farming and trade organizations, consumer groups, educational bodies, and financial institutions. Within these sectors, collaborative relationships among farmers, healthcare providers, veterinarians, laboratory experts, epidemiologists, sociologists, economists, wildlife conservationists, and communication specialists must exist. "One Health" approach also addresses that all relevant sectors should work together for developing legislation and policies, designing, and implementing control strategies. Interventions which jointly address human and animal health can increase health and economic benefits for communities, for example, sharing of human resources, equipment, and transport across sectors can reduce operational costs which increase cost-effectiveness.

Disease eradication programs consist of intensive surveillance which includes farm visits, systematic testing of individual cattle, and removal of infected animals along with the segregation of animals in contact with the infected one similarly in control of animal movement. The identification of infected animals or infected carcass prevents unsafe meat from entering the food chain and allows veterinary services trace back to the infected herd. Pasteurization of milk and meat inspection system should be strengthened and designed to prevent the consumption of contaminated products by people. Vaccine is used in human medicine, but it is not widely used as a preventive measure in animals because its efficacy is variable and it can interfere with testing to eliminate the disease. Thus, the establishment of new TB drugs which can be effective within a short term and capable of controlling the emergence of MDR-TB and XDR-TB is critically urgent.

8. Conclusions

Animal and human health is intimately interwoven and food animals serve as a reservoir of diseases of public health significance [74]. Animals with a contagious disease remain in the population and serve as a reservoir of infection for other animals and human beings. Therefore, the development of vaccines for animals against bovine tuberculosis is highly effective for TB control or development of recombinant BCG with expressing luciferase activity can be used as the most effective tool to advance drug development. The screening of TB in human or animal population is a very time-consuming process as *Mycobacterium* grows very slowly; conventional drug screening takes more than 3 weeks and the biosafety level-3 (BSL-3) facility is the basic requirement. Therefore, it is the need of an hour to develop rapid diagnostic procedures which can detect the organism within a short period of time. Some successful efforts are being made for the development of a new screening method to identify TB drug candidates by utilizing luciferase-expressing recombinant *Mycobacterium bovis* bacillus Calmette-Guéren (rBCG) [75].

The risk due to zoonotic TB is significantly less in developed countries than developing countries, which is due to the milk pasteurization and effective bovine tuberculosis control programs. Therefore, food safety of animal-origin food is worth considering. Efforts to improve food safety include scaling up the heat treatment of milk and ante-mortem and post-mortem inspection of all animals entering the food chain which will not only reduce the risk of transmission but also bring substantial benefits for the control of other foodborne diseases. A healthier animal population leads to healthier food supply along with economic benefits and improvements in animal welfare. The epidemiology of bovine TB is well understood and effective control and elimination strategies have been known for a long time but the disease is still widely distributed and often neglected in most developing countries. The increase of this disease in such areas calls for stronger intersectoral collaboration between the medical and veterinary professions to assess and evaluate the scale of the problem, mostly when zoonotic TB could represent a significant risk. Developed countries which follow test-and-slaughter policies still are not able to completely eliminate infection in cattle because of wild animal reservoirs; therefore, they are now focusing on the wild animal vaccination. Therefore, the vaccine research and

development program should be taken into account for possible application of vaccines to the animals, particularly in developing countries. Disease surveillance programs especially in areas where risk factors are present in animals and humans should be considered as a priority.

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