Epidemiology of Zoonotic Tuberculosis and its Implications in Asia

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ABSTRACT

Mycobacterium tuberculosis, a gram-positive bacterium that causes tuberculosis (TB) in human is still a serious global health concern, especially in Asia where 22 high burden countries are responsible for 80% of the world's TB cases. There are more than 150 known species of M. tuberculosis. Due to its virulence, it is the world's second most infectious cause of mortality. Furthermore, it has a high contribution to the overall disease burden. Causative agent of TB in animals is Mycobacterium bovis which is responsible for zoonotic tuberculosis in humans. The death rates resulting from these mycobacterial infections are impacted by various factors, including insufficient healthcare infrastructure, socioeconomic inequality, a dense population, and co-infection. The tendency of these mycobacteria to escape host immune responses and establish persistent infections is one of the virulence factors that contributes to the severity of tuberculosis. India has a highest 21% of TB infections in overall prevalence in Asia following China has 14%, Indonesia 6%, Nigeria 5%, Bangladesh 4%, Pakistan 3%, other 13 high burden countries for TB contribute 16%, while rest of the world contributes 20%. The early detection, directly observed treatment short-course (DOTS), and vaccination programs such as Bacillus Calmette-Guérin (BCG) have been the primary control methods in Asian countries. However, obstacles like multi-drug resistant (MDR) and dense populations have made these approaches less successful. To control and completely eradicate the disease in future top priority should be given to providing access to high-quality care, upgrading the healthcare system, and tackling socioeconomic factors that contribute to tuberculosis, such as hunger and poverty. To effectively eradicate tuberculosis in Asia and globally, cross border collaboration including cooperation between governments, international organizations, and research institutes is essential.

Key words: Mycobacterium tuberculosis, Mycobacterium bovis, Zoonotic tuberculosis, Persistent infections, Prevalence of TB, Directly observed treatment short-course, Bacillus Calmette-Guérin

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1. INTRODUCTION

Nearly 2 million individuals every year fall victim to (TB), making it the world's second leading infectious cause of mortality. About 8 million new cases of tuberculosis are reported annually, with 80 percent of those infections affecting the working population which falls victim to mycobacterium. Twenty-two high-burden nations are responsible for 80% of the world's TB cases. China, India, Pakistan, Bangladesh and Indonesia account for half of the world's TB burden, while Sub-Saharan Africa has the highest incidence rate.

Overpopulation, poverty, and poor nutrition are predisposing factors in the spread of tuberculosis. Human immunodeficiency virus (HIV) has been blamed for a dramatic increase in tuberculosis cases in Sub-Saharan Africa in recent years. Multiple drug-resistant tuberculosis (MDR-TB) epidemics have caused widespread public concern in developed nations. According to the World Health Organization (WHO), a significant proportion of the worldwide TB burden in humans is related to the zoonotic spread of bovine TB with 142,000 cases causing 12,500 deaths annually (Zimpel et al. 2020).

2. HISTORY OF *MYCOBACTERIUM*

Mycobacteria are gram-positive, aerobic, or micro-republic bacteria that are very picky about their environment. The pigments produced by certain mycobacteria vary in color from yellow to orange, and in very rare cases, salmon pink. They are between 0.2-0.6 x 1 to 10 µm in size. There are more than 150 known species of mycobacteria which are further divided into two categories. Mycobacterial species which are pathogenic to people and animals are slow-growing species that take more than 7 days to develop noticeable colonies on media, whereas fast-growing species take less than 7 days and are often not dangerous (Metzger et al. 2010).

Death records from the seventeenth century show that TB was a major killer in Massachusetts between 1768 and 1773. By the turn of the nineteenth century, the TB pandemic in Europe had reached its height. TB first developed in Asia in the late 19^{th} or early 20^{th} century. Although the contagious nature of tuberculosis was known to Aristotle and Galen, it was not proven until Koch described the tubercle bacillus in 1882 and later Dormandy in 1999 (Barberis, Bragazzi, Galluzzo, & Martini, 2017).

Recent deletion analysis investigations have shown that either *Mycobacterium africanum* or *Mycobacterium canetti* is the natural ancestral member of the genus, from which other species arose (Metzger et al. 2010). Previously, scientists assumed that *Mycobacterium bovis* was the progenitor of *M. tuberculosis*. The bacterium *M. bovis*, which is responsible for bovine tuberculosis, may infect and cause illness in a wider variety of hosts, including humans. When horizontal gene transfer and significant recombination events are disregarded, the alienable sections of the genomes of mycobacterium tuberculosis complex (MTBC) members are approximately 99.95% identical, demonstrating that they have clonally developed from a common ancestor with the tuberculous bacterium *M. canetti.* Single nucleotide polymorphisms (SNPs), deletions of up to 26 kb, duplication of a few paralogous gene families, and insertion sequences are the only mechanisms by which these infections have developed, giving rise to a wide range of host tropism and pathogenicity.

3. INTRODUCTION OF *M. TUBERCULOSIS* AND *M. BOVIS*

TB complex mycobacteria share 99.9% genetic similarity and identical 16S ribosomal RNA (rRNA) gene sequences. The 4411,532 base-pair genome has 3959 protein-coding and six pseudogenes. All 2441 genes have functions, excluding 912 conserved hypothetical genes.

M. bovis is a slow-growing bacterium. This bacterium affects cattle, goats, bison, deer, and badgers. It causes bovine TB. *M. bovis* infects humans, pigs, cats, and dogs. *M. bovis* and *M. tuberculosis* can cause TB in humans (Zimpel et al. 2020).

4. PATHOGENESIS OF *M. TUBERCULOSIS* AND *M. BOVIS*

The immunological response in classic animal testing shows four infection stages. Pathogenic mycobacteria survive and multiply in macrophages during the first stage by stabilizing the phagolysosome at pH 6.2-6.3 and staying in the endosomal recycling channel, where they can get iron. Avoiding acidity requires the cord factor. Phagosomes acquire lysosomal proteins but cannot merge with them. Monocytes are transported to the infection site in the second phase. Monocyte-to-macrophage differentiation maintains mycobacteria. When antigen-specific T cells grow, mycobacterial proliferation decreases. Release activates macrophages and removes the phagosome maturation block. Nitric oxide synthase produces mycobacteria-toxic radicals. After removing the impediment, the mycobacteria-containing vacuole can be acidified, speeding up the process. If immune cells fail to stop bacterium growth, the sickness progresses to the final stage.

Infected macrophages produce large amounts of pro-inflammatory mediators such TNF, IFN-γ, IL-6, IL-11, IL-18, and IL-12. Anti-inflammatory cytokines include TGF- and IL-10. TB symptoms, including fever and wasting syndrome, stem from uncontrolled cytokine production. Wild animal tuberculosis is a zoonotic threat to people and domestic cattle.

In animals, Inhaled *M. bovis* replicates in alveolar macrophages. After a lung infection spreads, lymph nodes in the mediastinum or elsewhere, such as the head and neck, may become infected. The host's immune system attacks the intruder cell by cell. Inflammation forms granulomas. Tubercles, or sores, characterize tuberculosis. After that, a laminar structure resembling an onion slicer emerges around the granuloma. The granuloma's core cells die, leaving dry cottage cheese-like debris. Biting wounds can spread TB in naturally infected groups. Pulmonary infection from infectious aerosols may take time to develop. Thus, a chronic illness develops, and the infected animal may exhibit a range of symptoms, from asymptomatic to severe overt disease with systemic pathology. Respiratory infections stay latent, unlike wound infections, which progress quickly and create sores. Badgers at any stage of sickness can harm vulnerable hosts.

Badgers with many illnesses have best summarized the pathogenic chain. Grossly evident lesions are more common in the thoracic cavity, which contains the lungs, and in the head and body lymph nodes. The abdominal cavity is uninfected, although many other tissues and organs may be. Badgers disperse similarly. Saliva contains TB, which can infect bite wounds. Due to rapid progression, enlarged lesions, and extensive infection, pathogenesis may differ here. Infected bite sputum can cause tiny subcutaneous granulomas or large, skinless sores.

5. VIRULENCE FACTORS ASSOCIATED WITH *M. TUBERCULOSIS* AND *M. BOVIS*

Inhaled *M. bovis* replicates in alveolar macrophages. After a lung infection spreads, lymph nodes in the mediastinum or elsewhere, such as the head and neck, may become infected. The host's immune system attacks the intruder cell by cell. Inflammation forms granulomas. Tubercles, or sores, characterize tuberculosis. After that, a laminar structure resembling an onion slicer emerges around the granuloma. Granulomas lose their core cells over time. Most bacterial infections, such as those caused by *Corynebacterium diphtheriae*, *Escherichia coli* O157:H7, *Shigella dysenteries*, and *Vibrio cholerae* toxins, lack the virulence components of *M. tuberculosis*. Even without pathogenicity data, the virulence of *M. tuberculosis* can be assessed. Bacterial load or burden is the total number of bacteria in a host following

infection, which is another virulence factor. This stage changes the growth curves of *M. tuberculosis* virulence mutants that reduce animal bacterial loads. Histopathological morbidity studies may reveal a distinct category of *M. tuberculosis* mutations that alter virulence but not bacterial burden.

6. EARLY EVENTS OF TB DISEASE ONSET

Alveolar airways are a common entry point for *M. tuberculosis* in susceptible patients. This is where it presumably has its initial touch with macrophages in the area. Pneumocyte, which are more common in alveoli than macrophages, may be infected and survive by *M. tuberculosis* even when they are outside of the body. Dendritic cells, which are far better antigen presenters than macrophages and likely play a major job in activating T cells with *M. tuberculosis* antigens, also play a critical role in the early stages of infection. Alveolar surfaces include a glycoprotein called surfactant protein A, which may increase mannose receptor activation and hence improve *M. tuberculosis* binding and absorption. Surfactant protein D, which is also found in alveolae, binds to mannosyl oligosaccharide residues on the bacterial cell surface, preventing phagocytosis of *M. tuberculosis*. This may stop *M. tuberculosis* from engaging with macrophages through their mannose receptors. *M. tuberculosis* and other intracellular infections first dwell in the phagosome, an endocytic vacuole, upon entering a host macrophage. Multiple infections, including *M. tuberculosis, Listeria monocytogenes*, and *Leishmania* major, are more lethal in mice with mutations in the gene encoding macrophage-localized cytokine-inducible nitric oxide synthase. Activated mouse macrophages create reactive nitrogen intermediates (RNIs), which are the fundamental components of antibacterial activity. A noteworthy conclusion from the latter study is that *M. tuberculosis* penetrates human macrophages and suppresses Ca^{2+} signaling but does not do so when *M. tuberculosis* is destroyed or when *M. tuberculosis* cells are opsonized by antibodies. Increased Ca^{2+} levels were associated with trafficking in late endosomes, which in turn facilitated the formation of phagolysosomes. Cytokines, nitric oxide, the respiratory burst, and other host defensive responses may all be triggered by Ca^{2+}. By preventing Ca^{2+} elevations, *M. tuberculosis* can evade these defensive mechanisms in the host. Some research has also shown that *M. tuberculosis* would fare better if it could remain in an early endosome for as long as possible, since this would reduce the activity of $CD4^{+}$ T cells in the host's immunological response. During infection with *M. tuberculosis*, macrophages are said to produce less major histocompatibility complex class I (MHC-I) protein and display fewer MHC-II bacterial antigens (Chandra et al. 2022).

7. LATER EVENTS OF TB DISEASE ONSET:

Infected lung macrophages generate chemokines that attract pathogen-resistant neutrophils, lymphocytes, and monocytes. Later, lymphocytes and big macrophages develop granulomatous localized lesions. This method usually stops spreading of bacteria. As cellular immunity grows and removes bacillus-filled macrophages, fibroblasts, lymphocytes, and blood-derived monocytes surround the caseous core of the granuloma. Latent TB, often known as chronic TB, can remain dormant and non-transmissible for life. Cell-mediated immunity can eliminate the infection. Granulomas heal into microscopic fibrous and calcified lesions. If the infected person cannot control the lung infection or if their immune system deteriorates due to immunosuppressive medications, HIV infection, malnutrition, aging, or other factors, the granuloma center can liquefy, providing a rich medium for the revived bacteria to replicate uncontrollably. Live *M. tuberculosis* can still enter the lungs, create active pulmonary TB, and spread to other tissues via the lymphatic system and blood (military or extrapulmonary TB).
Researchers studied *M. tuberculosis* "persistence" in mice using two chronic infection models and found that the bacteria may either be stable in the absence of sickness or not cultivable. The bacteria used to represent chronic diseases may be alive but quiescent, reflecting a true latent state, or they may be

constantly dividing and dying. *M. tuberculosis* supports the second notion that growth and death are controlled. In a mouse model of chronic TB, isoniazid is a drug of choice to kill *M. tuberculosis*. Biochemical investigations demonstrate that *M. tuberculosis* intermediate metabolism switches from aerobic, carbohydrate-metabolizing to anaerobic, lipid-utilizing during chronic mice infections (Chandra et al. 2022).

8. EVASION STRATEGY OF *M. TUBERCULOSIS* AND *M. BOVIS*

M. tuberculosis replicates fast inside host. Apoptosis restricts the transmission of attenuated *M. tuberculosis* in macrophages. Dendritic cells gather bacterial antigens from apoptotic vesicles formed by infected macrophages to link innate and adaptive immunity. Antigens presented by dendritic cells may awaken latent T-lymphocytes. The virulent strain of *M. tuberculosis* suppresses apoptosis and promotes necrosis. Infected macrophages die adaptively. Pathogenic *M. tuberculosis* alters several cellular pathways, and investigations have demonstrated that the host's eicosanoid production pathways regulate macrophage death.

Effector proteins and lipids used by *M. tuberculosis* to obstruct host lysosomal transport are briefly discussed. Endosomal markers RAB5 and RAB7 are not recruited by NdkA, and phosphatidylinositol 3-phosphate is dephosphorylated by SapM69. The phagosome-preventing serine/threonine protein kinase PknG binds to the RAB GTPase RAB7L1. Five type VII secretion systems (ESX-1–ESX-5) are encoded by *M. tuberculosis* and are responsible for exporting substrates from the cell. Important for pathogenicity upon contact with macrophages are the effectors ESX-1 and ESX-3. Both EsxA (exported by ESX-1) and PDIM (a lipid found in the cell envelope) are known to disrupt the phagosomal membrane. However, the mechanism by which this occurs is unclear. *M. tuberculosis* can take up nutrients and deliver effectors to the cytosol via permeabilizing the phagosome. *M. tuberculosis* can take up nutrients and deliver effectors to the cytosol via permeabilizing the phagosome. In addition to affecting the necrosis and inflammasomes AIM2 (cytoplasmic sensor) and NLRP3 (Nucleotide-Binding Domain, Leucine-Rich-Containing Family, Pyrin Domain-Containing-3), *M. tuberculosis* effectors modify lysosomal trafficking. The GAS-STING pathway is activated when bacterial or mitochondrial DNA enters the cytoplasm, prompting the cell to produce more type I interferons and initiating the autophagy process. Members of the *M. tuberculosis* PE-PGRS protein family block autophagy, at least in human lymphatic endothelial cells, and cytosolic mycobacteria join to create cords that are immune to selective autophagy. Since *M. tuberculosis* does not generate a large amount of mitochondrial reactive oxygen species, this may contribute to the decrease in NADPH (nicotinamide adenine dinucleotide phosphate) oxidase activity and autophagy that characterizes *M. tuberculosis* infections relative to those caused by other bacilli. When macrophages are activated by interferon before infection, *M. tuberculosis* is less able to obstruct lysosomal trafficking routes. In contrast to the host defense mechanisms of apoptosis followed by efferocytosis, *M. tuberculosis* induces necrosis using chemicals such as CpnT (NAD^+ glycohydrolase), PDIM (Phthiocerol dimycocerosates), and iron overload. Macrophage mortality is also affected by type I interferon and the increased tissue inflammation caused by *M. tuberculosis*. To survive in different intracellular settings and avoid the antimicrobial defenses of macrophages, *M. tuberculosis* employs a wide range of strategies (Chandra et al. 2022). The following are virulence factors related to *M. bovis.*

8.1. MYCOBACTERIAL LIPIDS

The cell wall of mycobacterium is rich in lipids with an exceptional range of physiochemical properties. Some components involved in virulence are lipoarabinomannan, lipomannan, phosphatidylinositol mannosidase, trehalose-6,6'-dimycolate, phthiocerol dimycocerosate and phenolic glycolipids.

8.2. SECRETION SYSTEMS IN MYCOBACTERIA

Mycobacteria have a waxy cell envelope, and it controls the movements of molecules. Some specialized protein structures for this purpose are twin arginine transporter, ESX-transporter, and PE proteins: PE-PPE and PE-PGRS (Polymorphic GC-rich Repetitive Sequences).

8.3. LIPOPROTEINS

Its genome analysis has shown approximately 90 putative lipoproteins out of which mostly are part of the mycobacterial cell envelope and plasma membrane too. Their presence also contributes to the interaction of the host and pathogen.

8.4. IMMUNE EVASION MECHANISMS

Mycobacterium has a prominent ability to infect and reside within immune cells. It can also survive in the dynamic environment of the macrophage phagosome. Some immune evasion mechanisms of this organism are phagosome arresting, resistance to reactive oxygen and nitrogen species, and inhibition of apoptosis.
It is almost certain that most of the virulence factors of *M. bovis* are the same as those of the classical human TB organism, *M. tuberculosis*, as both organisms can cause identical clinical disease in humans and are genetically very similar (Collins 2001).

9. TRANSMISSION OF *M. BOVIS* IN ANIMALS

Bovine TB is typically seen in the throat and lung lymph glands. Thus, this disease-causing bacterium is spread by mouth and nasal emissions. Inhalation and ingestion cause most infections. Infected food and drink are another risk. Badgers and cattle may have bovine TB. In cattle, respiratory, infected milk, placenta, or ambient contamination may spread it. In farm buildings, badgers may transmit this illness directly via close contact with cattle grazing in infected badger-infested areas (Cousins 2001).

10. TRANSMISSION OF *M. BOVIS* IN HUMANS

Bovine TB is contagious to humans. Raw milk and inhalation can spread it. Due to eradication campaigns, it is rare in developed areas, but reservoirs of animals make eradication challenging. *M. bovis* belongs to risk group 3, which causes extrapulmonary TB in infants and toddlers, tainted milk. Thus, milk boiling and pasteurization limit intestinal transmission. Meat and abattoir workers still get airborne illnesses. Humans infect slowly. Tuberculin skin testing and interferon-gamma release assays to screen for this infection. *M. bovis* and TB share symptoms. Fever, nocturnal sweats, and weight loss are common. Symptoms vary by body component. In 2017, WHO reported 142,000 zoonotic TB cases and 12,500 deaths. The lack of routine bovine TB testing understates these statistics (Grange 2001).

11. EPIDEMIOLOGY OF *M. TUBERCULOSIS* AND ITS ZOONOSIS IN ASIA:

11.1. PAKISTAN

Pakistan has an underreported disease burden, with 181 TB cases per 100,000 persons estimated in 2008 and 81 new sputa smear (SS+) cases per 100,000. TB case detection rates have increased from 19% in 2002

to 84% in 2008, while the rate for newly diagnosed SS+ patients has increased from 13% to 74%. However, recent TB incidence estimates have increased case identification rates to 60% for all TB patients and 58% for new SS+ cases. Despite this, the number of TB patients discovered has increased dramatically in Pakistan because to the efforts of the National Tuberculosis Program (NTP), from 11,050 in 2000 to 248,115 in 2008, and treatment success rates have reached 91% as of 2007. From 1995 onwards, Pakistan adopted and piloted the World Health Organization's (WHO) Directly Observed Treatment Short-course (DOTS) strategy for TB, but the "Islamabad Declaration" declaring TB a national public health emergency did not lead to significant progress in TB control until the NTP was revived in 2001. The National TB Program (NTP) operates under the Ministry of Health to provide general coordination, policy direction, and technical advice for TB management, while the Provincial TB Programs (PTPs) and district health authorities are responsible for actual implementation. The NTP headquarters maintain solid communication channels with PTP directors and local TB program administrators. In 2003, the NTP and PTPs surveyed general practitioners (GPs) in the Lahore and Rawalpindi districts and discovered that just 3% of GPs were using the national recommendations for TB diagnosis and care, while 90% were using chest radiography. There were 115,463 physicians registered with the Pakistan Medical and Dental Council as of the end of July 2009, and 42,700 establishments (69% clinics and pharmacies and 550 private hospitals) were offering official and informal medical services.

Pakistan has 410,000 new TB recorded cases with 69,000 TB deaths reported annually. Pakistan ranks sixth internationally and has the highest TB burden of the 22 WHO Eastern Mediterranean Region members. The NTP and its collaborators plan to conduct a 2010 Pakistani TB sickness prevalence research to better understand the problem (Chakaya et al. 2021).

Of 248,115 SS+ cases in 2008, 99,670 were new. The 2007 treatment success rate of 91% of new SS+ patients exceeded the WHO aim of 85% because of a decrease in the default rate to under 4% and low mortality, failure, and transfer out rates (2%, 1%, and 2%, respectively). Since 2007, notification growth has halted. Since then, only Punjab province has experienced a large increase in registered cases, while other districts have seen stable or declining numbers (Metzger et al. 2010).

The World Health Organization reports approximately 500,000 new TB cases each year, with the trend of drug-resistant cases rising. Pakistan accounts for 61% of Eastern Mediterranean WHO TB cases, contributing to the global TB burden. Data collected from Pakistan by WHO's Global Health Observatory has shown an average of 312,222 new and relapse TB cases each year over the past decade (Awan et al. 2022). In the last decade, TB cases were constantly increasing as in 2010, 264235 cases were recorded which further reached up to 356390 in 2016. Later, the disease incident rate remained constant until 2020 (Awan et al., 2022).

Approximately 5.75 percent of cattle and buffalo in Peshawar, Khyber Pakhtunkhwa, have bovine TB. Human sputum PCR indicated 96% *M. tuberculosis* and 4% *M. bovis*. A comparative cervical intradermal tuberculin (CCIT) test on large ruminants in five Central Khyber Pakhtunkhwa districts, Peshawar, Charsadda, Nowshera, Swabi, and Mardan found 5. 88% (141/2400) bovine TB.

Lahore, the second largest city in Pakistan, had 54% bovine TB by PCR. This study suggests government intervention to reduce TB's health effects. Animal farmers require awareness too. Cattle are more susceptible to this disease than buffalo, 6.45% vs. 5.28%. Infected cattle milk can spread *M. bovis*. PCR helps cattle detect *M. bovis.* 556 cattle and buffalo in Peshawar had bovine TB tested. 5.75 percent of 556 animals tested were positive. Whether 0the animals were farm-raised or bought, whether they slept indoors or outdoors, and how many were in the herd affected prevalence. *M. bovis* was tested in 92 retail milk samples. Eight of the ninety-two milk samples had *M. bovis*. 39.6% of participants knew that a three-week cough could indicate TB. Participants thought prayer and healthy nutrition (41.8%), natural therapies (35.7%), and contacting Hakeem (35.7%) could cure TB (Khattak et al. 2016).

11.2. INDIA

India has the world's largest TB burden with 3 million patients and 2 million new cases per year. Human tuberculosis reporting and bovine population and ownership in India highlight the need to address zoonotic risk from bovine TB. Buffalo-rich areas have higher household TB risk than buffalo-poor ones (Willgert et al. 2023). TB kills 280,000 Indians annually. India is second to China in MDRTB cases, with 99,000 cases per year (Claiborne et al. 2012). India has a highest 21% of TB infections in overall prevalence in Asia following China has 14%, Indonesia 6%, Nigeria 5%, South Africa 5%, Bangladesh 4%, Ethiopia 3%, Pakistan 3%, Philippines 3%, other 13 high burden countries for TB (HBCs) 16%, other countries 20% (Kashyap et al. 2013).

New Delhi had 1.1% fewer MDR TB cases in 2008-2009. 20.4% of 196 New Delhi patients with pulmonary TB who had failed earlier TB therapy, relapsed after treatment, or defaulted during treatment developed MDR TB in a 2005-2008 study. According to the Revised National Tuberculosis Control Programs (RNTCP), 20% of Indians have latent TB (Ahmed and Hasnain 2011).

M. bovis is thought to cause 10% of all TB cases in developing nations, posing a global health threat. *M. bovis* caused 25% of pediatric TB. Indian researchers searched scholarly journals for cow and buffalo bovine TB prevalence on September 11, 2017. Quantitative analysis used 82,419 bovine TB prevalence data from 1942-2016 research. 29,037 were buffaloes and 53,382 cows. This meta-analysis comprised previous studies. Incidence rates were estimated. Significant regions were sampled. Following is the data about some states of India showing prevalence of *M. bovis* from 2014-2016:

- Punjab (with a sample size of 121) had reported prevalence of 14%.
- Uttar Pradesh (sample size of 245) showed prevalence of 14.3%.
- Gujrat (sample size of 2310) reported 2.3% prevalence.
- Karnataka (sample size of 45) reported 26.7% prevalence.

In a recent study conducted in Guwahati metropolitan city India, it is shown that occurrence of bovine tuberculosis was highest in animals five years old and above (17.18%), followed by animals belonging to age group of 3 to 5 years (7.14%) and it was lowest in the age group between one to three years of age (6.52%). During the present study, 220 Jersey crossbreeds, 38 Holstein-Friesian (HF) crossbreeds and 102 indigenous crossbreeds of cattle were screened. The prevalence was found to be more in HF crossbreeds (13.15%), followed by Jersey crossbreeds (10.90%) and indigenous crossbreeds (8.82%). Prevalence of bovine tuberculosis in cattle showing symptoms which could be bovine TB (chronic coughing, reduced milk yield, emaciated body condition, respiratory distress, and fever) was found to be higher (19.71%) compared to apparently healthy cattle (4.58%) and is statistically significant (Srivastava et al. 2008).

11.3. RUSSIA

The Beijing BO/W148 clone of mycobacterium is widely distributed in the Commonwealth of Independent States (CIS) and Eastern Europe. It is most common in Siberia and the European region of Russia (to a lesser degree) (Mokrousov 2013). The spread of multidrug-resistant TB has strong ties to the corrections system. Using restriction fragment-length polymorphism analysis and spoligotyping, researchers analyzed 144 TB isolates found in inmates at the Archangel prison (Archangel, Russia) in 2001. Research of the genetic makeup of the isolates pointed to the W-Beijing group accounting for 87 (76.3%). Only 26.9% of the isolates were not found to be grouped in any way around the W-Beijing area. Toungoussova et al. (2003) found that there were 43 patients in the greatest cluster. Overcrowding, lack of air, and prisoners' generally poor health all contribute to the rapid development

of TB in prisons. There were 3,174 new cases and 171 fatalities from TB in Russian prisons in 2001, and the situation is worse when the illness is caused by drug-resistant *M. tuberculosis* (Toungoussova et al. 2003).
The rate of TB among the general population (not including inmates) in the Archangel region in northwest Russia decreased from 48 cases per 100,000 people in 2000 to 20 cases per 100,000 people in 1991. From 1996 to 2000, the incarceration rate-weighted incidence of TB climbed from 55 to 104 per 100,000 people, according to epidemiological statistics. This dramatic rise in TB cases may be traced back to the large jail population (Toungoussova et al. 2003).

11.4. CHINA

Large-scale population-based study on tuberculosis molecular epidemiology in China, with the second highest global prevalence. Nine drug-sensitive Chinese *M. tuberculosis* isolates shared spotlighting and Mycobacterial interspersed repetitive units-variable number tandem repeats (MIRU-VNTR) characteristics. School TB patients have unique disease experiences due to educational systems and socioeconomic circumstances, according to a qualitative study (Li et al. 2021). The northern pig-tailed macaque is a Class I protected mammal in China and a vulnerable species on the international union for conservation of nature (IUCN) Red List. In 24 provinces, milu deer breeding programs have saved them from extinction. China's latest animal quarantine law lacks disease surveillance and efficient quarantine. Quarantine before mixing with other animals and annual disease testing are recommended to protect animal health. The approved deer and monkey test, tuberculin skin test (TST), sometimes misses TB in monkeys. Faeces, urine, and hair should be sampled for disease detection, diagnosis, and surveillance (Chen et al. 2023). Rural extrapulmonary TB is more common in younger, female patients. Extrapulmonary TB patients have greater MDR-TB. Lymph glands, bronchi, bones, braces, urogenital tract, and meninges are affected. Extrapulmonary TB is less contagious and infrequent. Because it can affect any organ, its vast range of clinical symptoms makes diagnosis and treatment difficult. Extrapulmonary TB affects diabetics, HIV patients, and others. Women and individuals from high-TB-prevalence areas are more prone to get TB. Regional, population, and host characteristics affect anatomical positions (Pang et al. 2019). Diabetes reduces pleural TB risk but not extrapulmonary TB risk. In Poland and Romania, bronchial TB is most common, but in the Netherlands, US, and UK, lymph glands are. Due to Bacillus Calmette-Guérin (BCG) ineffectiveness against diverse TB strains, China's main extrapulmonary TB location differs from others. China's BCG immunization may be linked to extrapulmonary TB-affected areas.
Chinese ethnicity and residency affect BCG immunization rates. BCG immunization reduced severe tuberculosis in active TB patients. Severe active TB was rare in immunized people. BCG scars protected children from serious TB. Chinese law requires all newborns to receive the BCG immunization in the same hospital. However, private hospitals struggle to immunize newborns. Vulnerable children need newborn immunization programs, TB risk awareness, and BCG injections (Liao et al. 2022).
Recent transmission makes one in three TB patients' secondary cases. Secondary cases are more likely in MDR TB patients. Beijing strain-infected TB patients are more likely to be in a genomic cluster and develop active TB faster. *M. tuberculosis* dominates China. Intensified case discovery, fast tests with bacteriological confirmation, and suitable treatment can reduce *M. tuberculosis* spread. Isolating infectious TB patients, testing for latent TB, and providing prophylactic treatment may reduce TB rates. Improved diagnosis and screening reduce epidemic risks and prevent TB spread. Better boarding schools, teachers, and school doctors are needed. Controlling tuberculosis requires microbial genetic sequencing and epidemiologic methods, especially at universities (Li et al. 2021).

11.5. MALAYSIA

Tuberculosis (TB) is mainly found in underdeveloped countries and counts to be a major cause of morbidity and mortality due to a lack of diagnostic, prophylactic, and therapeutic tools (Nissapatorn et al. 2007). After starting the National Tuberculosis Control program in 1961 a reduction in TB cases was observed. A gradual increase was observed from early 1995 till 2002 with the highest incidence rate in Sabah state followed by Wilayah Persekutuan, Sarawak, and Pulau Pinang, respectively (Iyawoo 2004) (Aziah 2004) (Goroh et al. 2020). A large proportion of disease has been observed in foreigners living there. A study was conducted on patients from different walks of life admitted to the Institute of Respiratory Medicine (IRM) from May to December 2003. The rate of tuberculosis in this study was equally high in both native and nonnative patients (Nissapatorn et al. 2007). According to a survey, pulmonary tuberculosis is more prevalent than extrapulmonary tuberculosis (Swarna Nantha 2014). The population having diabetes mellitus is a major predisposing factor in the reactivation of tuberculosis, followed by smoking, chronic kidney disease/end-stage renal failure, and age-related issues (Swarna Nantha 2014). Age group, gender, and marital status also count be significant predisposing factors (Nissapatorn et al. 2007). To estimate the incidence rate in Sabah the State Health Department developed a protected electronic database (TB) (Goroh et al. 2020). DOTS (directly observed, treatment, short course) is the most effective treatment strategy available for controlling TB (Aziah 2004). Almost 33% of the world's human tuberculosis is found in the southeast Asia SEA. The most extensively recognized causing agent of human TB is *M. tuberculosis*, yet an ambiguous number of cases are due to *M. bovis* (Che-Amat & Ong, 2018).

Zoonotic tuberculosis is reported to be responsible for almost 3-15% of tuberculosis among humans worldwide and its infections are seen in a few SEA countries such as Malaysia and Thailand (Hassan 2014). A study conducted in Malaysian context show that if ruminant farmers are adequately up to date and educated, positive attitudes may increase higher levels of positive practices towards zoonosis (Sadiq et al. 2021). A recent study indicated that controlling the hunting of wild pigs and deer would help to control the transmission of infection from wildlife (Cantlay et al. 2017). Wild boars are known to contribute to the epidemiology of animal TB in some areas. Serology has been implemented for screening and diagnosis in wild boars and feral pigs due to relaxed procedures and quicker diagnostic outcomes (Lekko et al. 2021).

11.6. INDONESIA

In 2019, 10 million Indonesians had TB and 1.4 million died. The End TB Strategy has reduced TB infection and mortality slightly. Lack of care prevented 3.6 million TB diagnoses. Advanced disease (MDR) TB was difficult to cure and more likely to kill TB-infected patients. Lack of care may have prevented 3.6 million TB diagnoses. Sumatra has the highest TB prevalence at 95%. Due to their underdevelopment, Sumatra and Java have better health care. Males had more TB. The district had more TB cases than the province in Yogyakarta City. Urban areas risk TB. Environmental considerations make Central Java's Kendal District densely populated (Sulistyawati and Ramadhan, 2021). Indonesia's TB surveillance needs improvement. Due to a lack of healthcare workers, transportation, supplies, and knowledge, this could cause major issues (Noviyani et al. 2021).

Smoking increases the risk of chronic obstructive pulmonary disease COPD, including TB (Noviyani et al. 2021). Individual behaviour and family environment are predisposing factors for TB in Indonesia. Males are more probably to be exposed to TB risk factors, including smoking than females, with 33.8% of Indonesians aged 15 and older reporting smoking (Noviyani et al. 2021). Dogs and old-world monkeys are more susceptible to *M. tuberculosis* (Une and Mori 2007). Zoo animals may supply MDR-TB strains through invert zoonoses with *M. tuberculosis* (Kock et al. 2021). MTC causes wildlife TB in water, likely with *M.*

tuberculosis or *M. bovis*. It is widespread in Indonesia, Nepal, and Thailand, allowing human-to-nonhuman primate transmission. Diagnosis is needed to reduce wildlife tuberculosis (Che-Amat and Ong 2018). *M. tuberculosis* poses a risk of cattle to human transmission in resource limited countries (Adesokan et al. 2019).

11.7. MIDDLE EAST COUNTRIES

WHO's approach to eradicate tuberculosis includes early latent tuberculosis infection (LTBI) detection and control. Using a casual effects model, this study examined LTBI incidence and showed substantial heterogeneity. LTBI was 41.78% in Middle East and North Africa (MENA). To meet the WHO target of eliminating tuberculosis by 2035, MENA countries must increase tuberculosis control and LTBI detection (Barry 2021).

The MIRU-VNTR Act was assessed for its significance in TB control in Muslim Middle Eastern nations. Most Iranian and Saudi TB cases involved immigrants. Reactivated cases can spread harmful isolates. To prevent MDR-TB instances in receiving countries, immigrants must be screened for this disease and treated. According to studies, Saudi Arabia and Turkey were risky for adolescents. MIRU-VNTR molecular epidemiology studies will assess Middle Eastern TB control programs by measuring infection rates and effective factors. New tuberculosis cases, both reactivation and newly infected are considerable in each country, but reactivation is more relevant (Pourostadi et al. 2018).

World immigration centers in the Middle East. Migrants risk their health. Migrants cause health issues in both origin and destination countries. Due to discernment, linguistic and social barriers, legal status, and low socioeconomic level, immigrants can have serious fitness issues. Kuwaiti migrant laborers have a higher rate of pulmonary tuberculosis (Adhikary et al. 2011).

BCG vaccination and no tuberculosis mycobacterial (NTM) infection can skew TST results. The tuberculin skin test should be useful in most Middle Eastern states. TST will lose value in these states until BCG immunization is discontinued (Al-Jahdali et al. 2005). Bovine tuberculosis is a zoonotic illness that affects livestock and infrequently humans and is spread by local contact with sick hosts and unpasteurized dairy products. Bovine tuberculosis is a serious health threat across MENA, including developing nations. In the MENA region, bovine tuberculosis in humans and livestock varied widely by population size and state. Our findings show that the MENA region needs appropriate investigative gear and sustained regulatory approaches, especially on human and animal contact surfaces. MENA countries have reported human-only zoonotic tuberculosis (Kasir et al. 2023).

Iran's bovine tuberculosis records go back 50 years. Iranian hereditary cattle have bovine tuberculosis frequently. European livestock ranches now have a record 28% bovine tuberculosis prevalence. Bovine tuberculosis in Iranian sheep is unconfirmed. Typical TB lesions were isolated from sheep slaughter samples in 2003. Tuberculosis complex mycobacteria and microbes grew at 37°C. However, insufficient bacterial growth hampered molecular investigations to identify this isolate. In 2009, cicarin lymph nodes in Hoveizeh, Couzestan revealed an *M. tuberculosis* strain with a SIT587 spoligotyping. Reservoir animals' role in Iran's BTB epidemiology is uncertain and needs further study (Tadayon et al. 2013).

Despite the low prevalence of DM, 21% of tuberculosis patients in Yemen had DM. Most shared dominance studies were from Middle Eastern countries with rates ranging from 10% to 30%. A Saudi Arabian study indicated that diabetes/tuberculosis has more bone illness than non-diabetic TB. Two Turkish examples showed DM/tuberculosis patients with spondylitis and bone disease. In conclusion, DM/TB and non-DM/TB studies in the Middle East are scarce (Yosra and Abdely Scott 2010).

In 17 Middle Eastern countries, single, arbitrary, and multi-drug resistance in fresh and previously treated TB patients differs greatly. This comprehensive research suggests that drug-resistant tuberculosis, particularly MDR-TB, may be spreading in Middle Eastern TB patients. New fast diagnostics are utilized to

identify persons with tuberculosis symptoms, assess medicine vulnerability, and detect primary confrontation to first-line anti-TB drugs to achieve extra-operative tuberculosis control. To prevent further *M. tuberculosis* strains, efficient therapies must be found (Khademi et al. 2017).

12. CONCLUSION

Tubercle bacilli has gained more chances of infection spread as the immune system of people has been drastically reduced in low-income countries. The emergence and success of the antibiotic resistant mycobacteria has further worsened the situation. Mycobacteria has a vast range of hosts from humans to animals. So, to curtail the infection as well as to reduce the chance of zoonosis, medical and veterinary medical surveillances are needed to positively diagnose the disease outbreaks and later for its eradication.

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