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Prevalence, Types and Treatment of Tuberculosis: A Review

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Abstract

Tuberculosis (TB) is an infectious disease and one of the ten leading causes of death, globally. It ranks above HIV/AIDS in the number of deaths caused by a single infectious agent. According to WHO, about 1.4 million people died from TB in 2019. It is mainly an airborne disease caused by the bacterium Mycobacterium tuberculosis which spreads when the infected people exhale it into the air. The typical site of infection in TB is lungs (pulmonary TB), although it can also spread to the other parts of the body (extrapulmonary TB) such as the spinal cord, brain and kidneys. Pulmonary TB is the most common type of this disease. Despite its high prevalence, it is preventable and treatable. A wide range of treatment regimens are available. About 85% of patients recover from TB following a 6-month treatment programme. In recent years, the development of multidrug-resistant TB (MDR-TB) and extremely drug-resistant TB (XDR-TB) has presented new challenges for the treatment and management of this disease. The transmission mechanism of MDR-TB is the same as drug-susceptible TB. Drug resistance is a challenging obstacle in its prevention and care. It makes the treatment difficult and it takes a longer span of time to treat the disease. There is a need to develop fast diagnostic tests and an effective treatment against MDR-TB and XDR-TB.

Keywords: extremely drug-resistant (XDR), extrapulmonary tuberculosis, multidrug-resistant (MDR), *Mycobacterium tuberculosis* complex**,** pulmonary tuberculosis

Introduction

Tuberculosis (TB) is a lethal and infectious disease that has affected humankind over the past 5000 years. It is a major health burden, worldwide. About 9 million cases are reported every year and about one fourth of the infected patients die. The mortality rate is higher in adults. An increase of 2% is reported in the cases of TB every year and the number of the reported cases of drug-resistant TB is also escalating

at an alarming rate [1]. Also, many of the infected people are unaware of the fact that they are infected with it [2]. In 2010, the estimated incidence of TB was about 8 million. Deaths from TB among HIV-negative patients were 1 million, while deaths among HIV-positive TB patients were about 0.40 million [3]. The higher incidence rate (231/100,000 population) and the elevation of MDR cases in the country demands focus on various TB control strategies [4]. As per the recent report of the World Health Organization (WHO), the elevated rate of TB throughout the world was 9 million among the 7.1 billion people in 2013, which shows an occurrence rate (number of new cases reported in the population) of 126 cases in a population of 100,000 inhabitants. In Pakistan, approximately 297,000 TB cases are diagnosed each year and the country ranks fourth among high TB burden countries [5].

Common symptoms of TB are coughing with blood for 3 weeks or more and the presence of sputum in the lungs which causes pain in the chest. Only activated TB will conform to all the symptoms such as a reduced appetite, fever, weakness or fatigue, sweating at night and weight loss. Extrapulmonary TB includes TB meningitis, tuberculosis, lymphadenitis, pericardial TB, pleural TB and miliary TB besides pulmonary TB. Newborn babies and children with HIV appear to have a higher possibility of contracting extrapulmonary TB. The containment of TB is achieved through treatment as recommended by WHO and through a directly observed treatment short-course (DOTS) strategy. MDR-TB cases benefit from the DOTS strategy, MDR-TB is resistant to either one of the following drugs: isoniazid and rifampicin. [6]. In Pakistan, keeping in view the number of cases per 100,000 /inhabitants, the extent of TB weight is 231 [4]. WHO ranks Pakistan as fourth among high TB troubled nations [5]. This situation is disturbing for developing nations like Pakistan, as the majority of the casualties of TB were observed to be in their economically effective years of life. Pakistan is rated 6th among the most populated countries in the world with an area of 796,095 km^2 and a population of around 186 million. Tuberculosis remains a prevalent health issue in Pakistan. It is located in the Asian region that singularly produces 60% of TB cases. Out of 22 countries, Pakistan is ranked 5th among countries with high burden of TB [7].

2. Types of Tuberculosis

Tuberculosis can be comprehensively grouped into two main types. One is pulmonary TB and the other is extrapulmonary TB. Pulmonary TB affects lungs and remains more prevalent. When the disease is transmitted from the lungs to different parts of the body, which happens in around 15-20% of the instances of active TB, then it is referred to as extrapulmonary tuberculosis (EPTB) [8]. In this case, central nervous system, lymphatic system, kidneys, bone, and genitourinary framework are the frequently infected regions. EPTB can exist with PTB at the same time [9].

3. Route of Infection

In 1679, Franciscus Sylvius reported the lung knobs as "tubercula" (little bunches); however, it was considered to be a type of tumor or an irregular organ for quite some time. Benjamin Maten in 1722 made an initial hypothesis about the virulent nature of the disease. He suggested that TB is caused by the "animaliculae". The infection is transmitted from the affected individuals to healthy individuals. The infection begins by the inhalation of droplet nuclei. In 1865, Jean-Antonine Villemin explained the virulent nature of tuberculosis [10]. He effectively transmitted liquid from human and cow-like injuries to a rabbit that caused tuberculosis. His counterparts disregarded his discoveries until 1882, that is, when the activity of Robert Koch was reported. Koch effectively extracted and cultured mycobacterium from pulverized tubercles [11]. In 1890, he reported that the filtrates obtained by culturing may heal the infection. However, this statement was firmly disparaged at that time. [12]. Later on, Koch's filtrates were purified. Purified filtrates were utilized to develop the infection and this process is known as the tuberculin skin test.

4. Pathogenesis of Tuberculosis

The pathogenesis of TB can be explained in five phases. The principal phase is the ingestion phase which begins once a person breathes droplet nuclei having bacilli that reach the alveoli of the lung, the primary site for infection. Alveolar monocytes / macrophages ingest the bacilli and most of the bacilli are destroyed because of the immune response. The level of the eradication of bacilli depends upon the response of macrophages, the hereditary qualities and the virulence factor of the pathogen [13]. The majority of the alveolar macrophages

are activated non-specifically and destroy the breathed-in bacilli. On the other hand, if the macrophages in alveoli are unable to uproot the bacilli, the bacilli build up inside them and destroy them [14]. The second phase is the symbiotic phase. In this phase, macrophages keep on increasing without destroying tubercle bacilli. This increases the survival rate of the pathogen inside them. A limited quantity of tubercle bacilli enters into the circulatory system and is transmitted to every part of the body. The tubercle bacilli might reach anywhere in the body, where TB will probably grow (such as the brain, larynx, lymph node, lung, spine, bone, or kidney) [14]. Unfortunately, the majority of the macrophages / monocytes in the circulatory system are immature and are unable to process the tubercle bacilli after engulfing [14]. During this phase, macrophages and tubercle bacilli can't harm each other, they come together and make a lesion of tubercle.

The next phase is the caseous necrosis developing phase. As the number of tubercle bacilli increases to a point that is sufficient to initiate the tissue-harming DTH framework, the tubercle bacilli-loaded macrophages are destroyed. The passing macrophages make a strong caseous granulomas focus which is primarily covered by non-enacted or immature macrophages [13].

The fourth phase, an essential phase, is to figure out that the patient must have a clinically clear indication. It relies on the cell-mediated immunity (CMI) of the host. In case of a poor CMI, fringe macrophages can't ingest the remaining tubercle bacilli from the center of caseous necrosis, thus bringing on the broadening of the caseous center and the development of the disease. On the other hand, in case of a powerful CMI, the highly stimulated macrophages ingest and kill the leaving tubercle bacilli from the caseous necrosis lesion, after which the lesion stays in a subclinical phase [13]. In the last phase, which is the liquefaction phase, the tubercle bacilli grow extracellularly and multiply to numbers that can't be defended even in the case of a powerful CMI. The tubercle bacilli then kill the wall of the bronchi which allows them to infect the lungs or other parts of the body [14].

A major limitation of the TB control programs is the difficulty in the early and reliable detection of the bacteria in the samples. The microbiological and chemical tests currently in use are tedious and require many days and even weeks to detect the pathogen in clinical samples. The morphology of colony, nitrate reduction, resistance and

sensitivity to pyrazinamide and niacin tests are used to differentiate between *Mycobacterium tuberculosis* from *M. bovis* and *M. africanum* [15, 16, 17, 18].

5. Comparison of Active Disease and Latent TB Infection

Regardless of the infected region of the host body by *M. tuberculosis*, there are no infectious indications because of an effective host immune system [19]. Herein, *M. tuberculosis* does not show replication in vivo and is known as "latent tuberculosis infection" (LTBI). In the presence of the signs and symptoms of the disease and damage to the lungs, the condition is regarded as highly contagious [20]. Despite some similarities, there is a large extent of dissimilarities between an active TB infection and *M. tuberculosis* infection (Table 1). Figures 1(A) and 1(B) show the x-rays of the two types of tuberculosis. It is significant to distinguish between these two types for an accurate clinical assessment and case analysis.

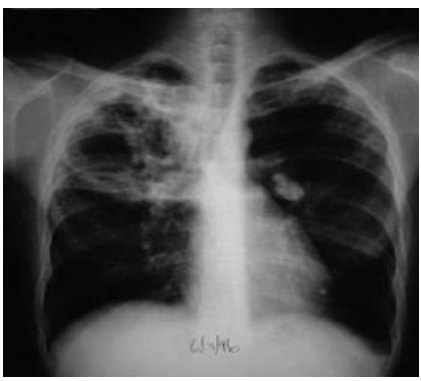

Figure 1(A). Chest radiograph showing pulmonary TB [21]

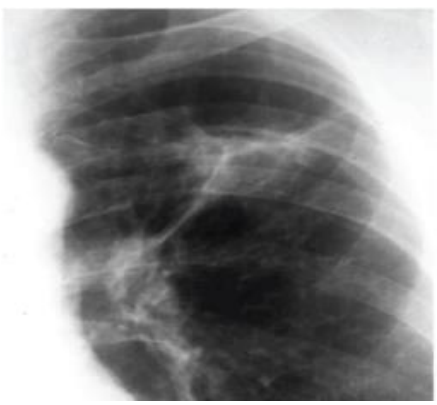

Figure 1(B). Chest radiograph showing active TB [21]

Table 1. Pulmonary TB and *Mycobacterium tuberculosis* Infection

Active Tuberculosis disease	***Mycobacterium tuberculosis* infection**
Presence of MTB	Presence of MTB
Sign and symptoms of TB are present	Absence of clinical symptoms
Sputum smear positive for Zn stain	Sputum smear test negative for Zn stain
Highly contagious	Not contagious
Sputum culture test is positive for MTB growth	Sputum culture test is negative for *M. tuberculosis* growth
Positive for tuberculin skin test	Positive for tuberculin skin test
Chest X-ray indicates lesions and causes lung damage	Normal Chest X-Ray
Chemotherapy for drug susceptible TB	Nine-month isoniazid monotherapy

Table 2. Active Disease and *Mycobacterium tuberculosis* Infection [21]

Active TB disease	***M. Tuberculosis* infection**
Presence of MTB	Presence of MTB
Signs and symptoms are present for TB	Absence of clinical symptoms
Sputum smear positive for Zn stain	Sputum smear test is negative for Zn stain
Tuberculin skin test is positive	Tuberculin skin test is negative
Highly contagious	Not contagious
Sputum culture test is positive for MTB growth	Sputum culture test is negative for MTB growth
Chemotherapy for drug-susceptible TB	Nine-month isoniazid monotherapy
Chest X-ray indicates lesions and causes lung damage	Normal chest X-ray

6. *Mycobacterium tuberculosis* Complex

Different mycobacterial species which show close resemblance with each other are part of the *M. tuberculosis* complex (MTBC). Most important types of *M. tuberculosis* complex include *M. tuberculosis, M. bovis* and *M. africanum*. Apart from a few differences in their host series, morphology and destructiveness, they show a high hereditary resemblance with each other [22].

6.1. *Mycobacterium tuberculosis*

TB in human beings is caused by a mycobacteria, namely *Mycobacterium tuberculosis.* People who have pulmonary or laryngeal TB produce infectious airborne droplets while coughing, wheezing, and talking. Infectious droplets breathed in by individuals stay in the alveoli and there the bacilli are taken up by the macrophages, beginning a progression of stages that result in either the control of the disease or the movement to the next stage which is the active stage [23]. The distinguishing feature of all *Mycobacterium* species that separates them from other bacteria is their thick cell wall. It consists of extraordinary glycolipids that may give protection and resistance against anti-infection agents [24]. It shows extremely slow growth as compared to other bacterial species. *M. tuberculosis* stays alive and multiplies inside the host macrophage cells. Despite broad research, little information is available about the pathogenicity of *M. tuberculosis*. Indeed, *M. tuberculosis* produced artificially is different from *M. tuberculosis* extracted in vivo in various manners [25]. To spread the disease and to set up their pathogenicity, microorganisms should leave their hosts. Similarly, the mechanism of the escape of *M. tuberculosis* from the macrophage cells is a unique process [26]. It has developed approaches to leave behind the host immune framework, permitting it to survive inside the macrophages. It opposes the activity of receptive oxidative radicals inside these cells, which exhibits its survival strategy and also its ability to cause disease inside the host [27]. It is known for causing cell death of infected human macrophages and uses exceptional (*M. tuberculosis* particular) signals for the transportation of protein inside the host [28]. It is crucial to be familiar with the procedure included in *M. tuberculosis* determination and existence inside macrophages and how it spreads the disease to different hosts [29]. Figure 2 shows the stages of *M. tuberculosis* infection.

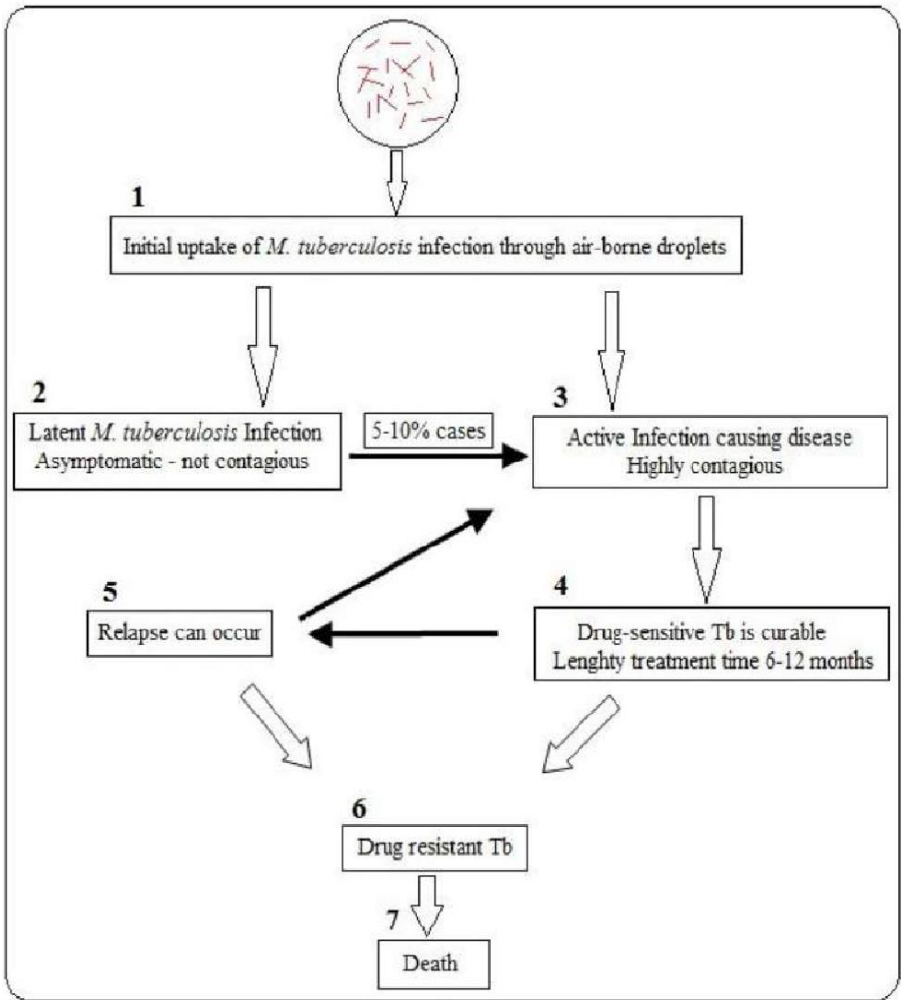

Figure 2. Steps of *M. tuberculosis* infection

(1) Inhalation of *M. tuberculosis* cells through airborne droplets builds up the disease in the host.
(2) Contingent upon the number of cells inhaled and the ability of the immune response of the host (section 1.2), active state infection can't happen for quite a long while.
(3) It may be converted into an active infection causing disease.
(4) Drug-sensitive TB is curable but requires a lengthy treatment.
(5) Relapse can occur.

(6) Due to the absence of perfect treatment, drug-resistant TB can build up.
(7) *M. tuberculosis* doesn't respond to the existing chemotherapy in various drug-resistant cases, causing death [30].

6.1.1. Morphology of *M. tuberculosis.* Mycobacteria are non-motile, aerobic, slightly bent or straight rods with a width of 0.2-0.6μm and they usually do not form spores [31]. Generally, bacteria can be classified into gram-positive and gram-negative types based on the staining process. This process doesn't apply to mycobacterium. The unique characteristic of the cell wall of mycobacterium is that it provides resistance against the Gram stain. *Mycobacterium* will appear as a gram-negative, fast growing clear area within the bacterial population or it may appear as gram-positive rods or beads [32].

6.1.2. Classification. Mycobacterium can be categorized on the basis of their growth rate into two groups. If it takes it seven days to grow, then it is considered as a fast grower and if it takes a longer time period to grow, then it is considered as a slow grower. On the basis of photo-reactivity, mycobacterium can be divided into three groups which include photochromogens, scotochromogens, and non-photochromogens. Photochromogens produce colored colonies only when light is available. If they produce pigmented colonies themselves in the absence of light, they are considered as scotochromogens. Non-photochromogens are the ones which do not produce any pigmented colonies with or without light [32].

6.1.3. Cell Wall. The cell wall of *mycobacterium* is made up of peptidoglycans and lipids. It consists of glutamic acid, arabinose, opimelic acid, glucosamine, muramic acid, alaine, meso-diamin and galactose [33]. Additionally, it consists of a hydrophobic mycolate layer and other free lipids such as trehalose-6, 6'-demycolate that provide hydrophobic permeability barrier to its cell wall and lower the permeability of many compounds [32]. This hydrophobic permeability barrier provides resistance against many antimicrobial agents and also prevents engulfing by macrophages. At room temperature, through the use of a 2% aqueous glutaraldehyde solution suitable bactericidal efficiency can be attained [34]. A main factor behind *M. tuberculosis* cell wall related pathogenicity is its high impermeability and a thick waxy layer [35]. It acquires some exceptional lipids such as lipoarabinomannan (LAM) which are connected to the cell membrane

and are thought to be linked with its virulence and resistance [36, 37]. LAM is associated with the pathogenicity of *M. tuberculosis* in various ways. For example, LAM serves as a ligand in *M. tuberculosis* virulent strains including H37Rv and Erdman strains to bind mannose receptors used for virulence-associated intracellular trafficking [38].

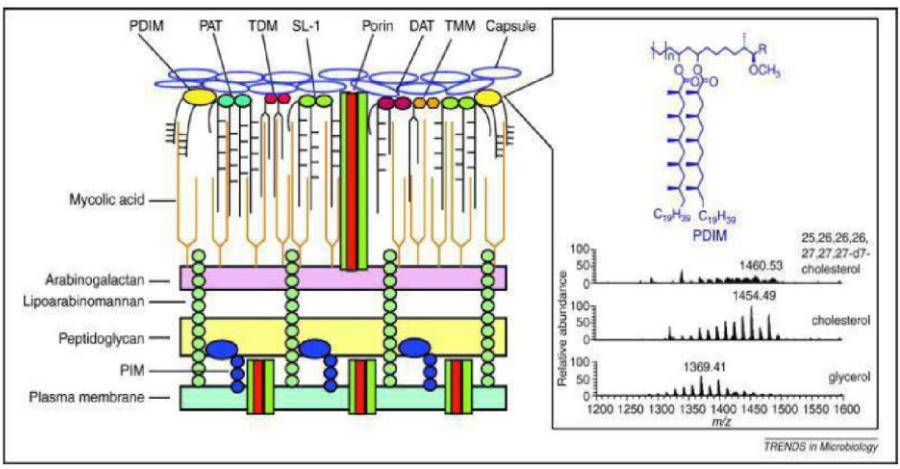

Figure 3. Structure of the *mycobacterium* cell wall [33]

6.2. *Mycobacterium Bovis*

Bovine tuberculosis was initially reported in 1929 in kudu and regular duiker in South Africa. In the 1940s, the infection was observed to be contagious in kudu. *M. Bovis* is a zoonotic life form and in order to avoid infection in humans, it ought to be dealt with as a risk group III organism with proper precaution. Bovine tuberculosis is an infection that affects domesticated animals such as cattle, buffalo and pig and certain free or captive wildlife species. It is generally portrayed by the development of nodular granulomas known as tubercles. Lesions are most often seen in the lymph hubs (especially of the thorax and head), lungs, digestive system, peritoneum, liver, pleura and spleen, although tissue can also be affected [39].

6.3. *Mycobacterium africanum*

Among the most important members of the *M. tuberculosis* complex causing human pulmonary TB is *M. africanum* [40, 41]. It may cause infection in different parts of the body such as mucosa and skin [42, 43]. It also shares a high hereditary similarity with *M. tuberculosis* [40, 41]. Castets *et al*. in 1968 initially recognized *M. africanum* between

West-African strains. Phenotypic variations are responsible for its further subdivision into *M. africanum* subtype I (West-African) and subtype II (East-African) [44, 45].

6.4. *Mycobacterium leprae*

Mycobacterium leprae has a close resemblance with *M. tuberculosis and* causes leprosy [46]. It has a long history of affecting human beings [47]. Leprosy principally influences skin and peripheral nerves [48]. The transmission of the disease is primarily due to the nasal droplets and its DNA may be present in healthy people [49, 50]. Outside of the host's body, *M. leprae* shows resistance to a wide variety of natural stresses [51]. Understanding the basic knowledge of *M. leprae* infection, its transmittance and spread is imperative for the better control of infection and disease elimination [52].

7. Tuberculosis Strains and Drug Resistance

TB strains are grouped into two types based on their resistance against available drugs. These include multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. MDR strains demonstrate resistance against anti-TB drugs of the first-line, that is, INH and RIF. XDR strains show resistance against any fluoroquinolone or capreomycin, kanamycin, and amikacin and also show resistance against INH and RIF just like MDR-TB [53, 54]. Gene loci involved in conferring drug resistance in *M. tuberculosis* are given in Table 3.

Table 3. Gene Loci Involved in Conferring Drug Resistance in *M. tuberculosis* [55]

Drug	Gene	Product	Reported frequency in resistant strains (%)
Rifampicin	*rpoB*	B-subunit of RNA polymerase	>95
Isoniazid	*katG*	Catalase-peroxidase	60-70
	OxyR-αhpC	Alky hydro-reductase	~20
INH-ethinoamide	*inhA*	Enoyl-ACP reductase	<10

Drug	Gene	Product	Reported frequency in resistant strains (%)
Streptomycin	*rpsL*	Ribosomal protein S12	60
	Rrs	16s rRNA	<10
Fluoroquinolones	*gyrA*	DNA gyrase	>90
Pyrazinamide	*pncA*	Amidase	70-100
Ethambutanol	*emb*CAB	EmbCAB	69

8. Multidrug-resistant Tuberculosis

Multidrug-resistant TB (MDR-TB) encompasses a relatively brief time (4 to 16 weeks) from diagnosis to death and is connected with a high mortality ratio of about 50% to 80% [56]. Poor treatment and late recognition of drug resistance are the central reasons adding to MDR-TB outbreaks, particularly in health care facilities [57, 58]. In individuals receiving inefficient drug treatment of TB, some bacteria survive the treatment. These bacteria give rise to strains resistant to a particular drug due to spontaneous mutation. These mutated bacteria serve as a source for the drug resistant population. In case of poor treatment, this population can further develop resistance to other drugs, consequently leading to XDR. MDR-TB cases in this manner might emerge due to insufficient recovery of a person who was at first infected by a completely sensitive strain or a single drug-resistant strain [59].

9. Treatment of MDR-TB

The strains of *M. tuberculosis* resistant to both RIF and INH are termed as multi drug-resistant TB (MDR-TB). For the initial 6 months, MDR-TB is treated with 5 to 6 drugs and afterwards, 3 to 4 drugs are used for long-termtreatment. A total duration of 18 months is required for the treatment, yet the optimal duration has not been identified. The first-line anti-TB drugs such as pyrazinamide (PZA) and ethambutol (EMB) are used to treat MDR-TB

9.1. Rifampicin

Rifampicin interferes with mRNA synthesis by binding with RNA polymerase [60]. Mycobacrteria develops resistance if there is mutation

in a particular region for the RNA polymerase subunit. The gene *rpoB* if mutated is responsible for most of the resistance in mycobacteria [61].

9.2. Pyrazinamide

Pyrazinamide (PZA) was discovered in 1952 and remains a standard TB treatment drug. It is similar to nicotinamide. PZA actively takes part in sterilizing and kills most of the rod shaped bacterium in the intensive phase of the treatment [62]. The duration of TB treatment is shortened from 12 months to 6 months because of its addition in the treatment therapy [63]. It is biologically inactive and needs to be changed into its operating type, that is, pyrazinoic acid through the catalysis of the enzyme pyrazinamidase. *pncA* gene is known to encode PZase. PZA needs an acidic medium for activation. Once activated, it agglomerates in the cytoplasm bringing down the intracellular pH to the level which shows the inactivation of the fatty acid synthase [64]. Mutations providing resistance to PZA activity are dispersed completely on the *pncA* gene [65, 66, 40].

9.2.1. Mode of Action of PZA. PZA is proposed to be a prodrug like INH on the basis of PZA studies. It shows no activity against *M. tuberculosis* unless activated. A specific enzyme is required to activate it and convert it into an active form. Isoniazid (INH) is another prodrug used in the treatment of *M. tuberculosis*. It is a well-known prodrug. Through the action of the enzyme (mycobacterial catalase peroxidase), which is encoded by *KatG* gene, INH is converted into its active type. The active form of INH damages *M. tuberculosis* by changing the biogenesis of mycolic acid within the cell wall of the mycobacterium [67]. In the same way, PZA moves into cytoplasm through passive diffusion. Here, PZA is converted into its active type, that is, pyrazinoic acid (POA) with the help of an enzyme pyrazinamidase. This enzyme is produced by *M. tuberculosis*. POA then becomes inactive and diffuses out of the cytoplasm. If the pH of the extracellular environment is around 5.5, then POA is protonated. Afterwards, HPOA simply moves through the membrane of *M. tuberculosis*. It again moves into the cytoplasm causing cytoplasmic acidification. This acidification stops the trans-interpretation of targeting on non-replicating persisters ribosomal protein S1 [68, 69] and destroys the activity of the membrane of MTB (Table3) [70].

10. Extremely Drug-resistant Tuberculosis

In 2005, extremely drug-resistant tuberculosis (XDR-TB) was initially reported around the world [71, 72]. XDR-TB is connected with poor treatment results [73]. XDR-TB strains are made when MDR-TB is poorly treated, which amplifies second-line drug resistance. Lack of treatment for XDR-TB may bring about extra resistance, seriously restricting the choices available for viable treatment. The reasons behind XDR-TB are complex and incorporate improper treatment regimens, violations of disease treatment, late determination of the disease, and reduced disease mechanism [74, 75].

11. Treatment of Tuberculosis

WHO proposed applying a stringent directly observed therapy short-course (DOTS) strategy to manage the developing burden of TB after declaring it as a health crisis in 1993 [76]. A series of synergistic antibiotics are given to the drug-sensitive TB patient (Table 1.2). These antibiotics are used for an ideal treatment to cure the infection and to avoid relapse [77]. Both types of infection namely active TB and latent tuberculosis infection (LTBI) are curable; though, patient adherence to the given treatment is essential for complete cure. Disease burden can be reduced considerably by treating LTBI [78]. First line and second line anti-TB remedies are useful in treating MTB diseases. Before and during the treatment, the testing of the bacterial culture and its susceptibility are necessary to identify the selective design of *M. tuberculosis* with a specific end goal in order to properly adjust the course and dosage of antibiotics [79]. Proper combinations of typical frontline and reserved anti tuberculosis remedies are given on the basis of the kind and phase of infection.

11.1. Standard TB Drugs

The available TB treatment consists of isoniazid (INH), rifampicin (RIF), streptomycin (STP), ethambutol (ETH), and pyrazinamide [80]. Most of the first-line and second-line anti tuberculosis drugs listed in Table 3 and shown in Figure 3 perform bactericidal action. They act against MTB. Second-line drugs are not used because of the concerns about their safety; however, when combined with the first-line drugs, they show better results particularly for curing drug-resistant TB [81]. Reserve classes of these drugs are developed from different antibiotic classes, for example cycloserine, *p*-aminosalicylic acid, thioamides,

aminoglycosides, and fluoroquinolones. Chemical assemblies of the first-line drugs are shown in Figure 4.

Table 4. Standard Anti-tuberculosis Drugs, Target, Year of Discovery and Activity [70]

First-line drugs			
Drug	**Target**	**Discovery Year**	**Activity**
Ethambutol	Cell wall	1962	Bacteriostatic
Pyrazinamide	Ribosomes	1952	Bactericidal
Isoniazid	Cell wall	1952	Bactericidal
rifsmpicin	RNA polymerase	1963	Bactericidal
Second-line drugs			
Ciproflaoxin	DNA gyrase	1987	Bactericidal
Ethionamide	Cell wall	1956	Bacteriostatic
Amikacin	rRNA	1970	Bactericidal
Aminosalicyclic acid	*thy* A gene	1949	Bacteriostatic
D-cycloserine	Cell wall	1955	Bacteriostatic
Streptomycin	Ribosomes	1944	Bacteriostatic
Capreomycin	Ribosomes	1960	Bactericidal

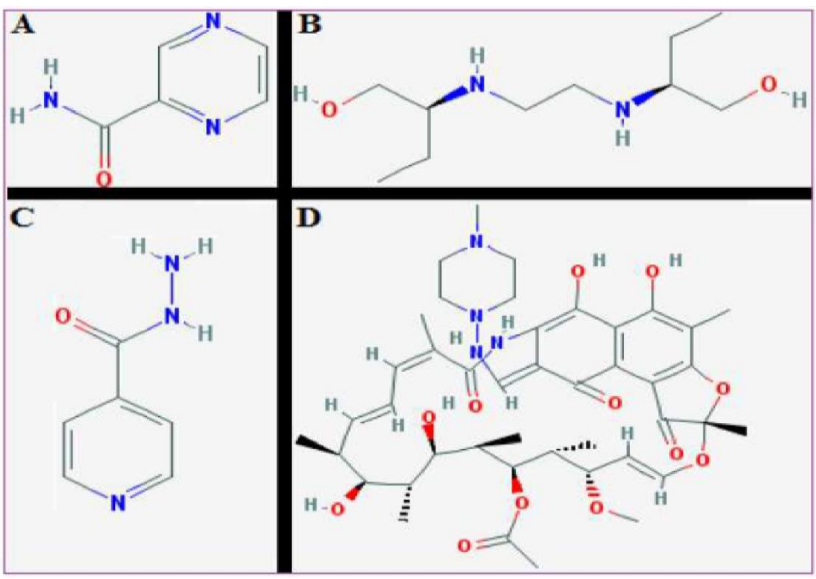

Figure 4. Recent groups of the drugs of TB responsible for front-line defense (A) Pyrazinamide: molecular formula C5H5N3O and

molecular weight 123.11 g/mol (B) Ethambutol: molecular formula C10H24N2O2 and molecular weight 204.30 g/mol (C) Isoniazid: molecular formula C6H7N3O and molecular weight 137.13 g/mol and (D) Rifampicin: molecular formula C43H58N4O12 and molecular weight 822.94 g/mol (chemical structures of drugs recovered from the PubChem database).

12. Immune System and Tuberculosis

The response of the immune system to TB infection is complicated. The elements of the immune system involved are T cells (CD^{+4} and CD^{+8}), macrophages and cytokines (TNF-α, IFN-γ, IL- 6 and IL-12) [82]. Immune response is different in the case of a persistent and severe infection. There are four stages of pulmonary TB. The first stage is the ingestion of tubercle bacillus by macrophages. It destroys the bacilli placed in an incubator for a period of 4 to 12 weeks after the microphages ingest the alveolar bacilli. The process depends on the inherent microbial capability of the host phagocytosis and the virulence factors of the engulfing mycobacterium. Mycobacteria which eject out of the initial step go through the second stage where three scenarios can arise. The first scenario is based on the host pathogen-relationship, where the host contains the pathogen and the pathogen dies. In the second scenario, mycobacterium spreads in the whole body when the host immune response is low (usually in immuno-suppressed patients) which leads to active infection. The third scenario is when the host immune response and the virulence factors of MTB are equalized and within the macrophages, intracellular bacteria are suppressed. Disruption of the macrophages attract blood monocytes and other inflammation cells to the alveoli. At this stage of the infection, a lower rate of tissue damage occurs. After 2 to 3 weeks of infection, the rise in the antibodies particularly T lymphocytes within the premature infection occurs. Isolation is achieved at the main site of infection by granula formation in the host immune system. The granula contains T-cells such as CD^{+4} and CD^{+8} cells in addition to the Beta cells. Moreover, fibrousblasts and additional cells are present within the granula [46]. The granula helps to limit the growth of the disease by isolating the bacteria from the rest of the lung, thus limiting and facilitating the activity of the immune system. The early bacilli cease to grow at beginning of the third step of pulmonary infection [83]. Solid necrosis is the most important infection and it inhibits the extracellular

development of mycobacterium and its lesions for many months and years. In the last stage, any disruption in the host and pathogen relationship results in the weakening of the cellular immune system, thus causing endogenous exacerbation leading to active TB. Engulfing may lead to the breakdown of the nearest bronchi causing the bacilli to grow to the other parts of the lungs or to the host's other organs.

13. Conclusion

TB is a high burden disease which is common in developing countries. Many factors contribute to its spread in these regions such as malnutrition, poor ventilation, overcrowding and the existence of immunocompromised patients. All these factors are linked to poverty. Poor treatment and lack of proper diagnosis has led to the emergence of drug-resistant tuberculosis. Advanced diagnostic tests, new preventive chemotherapies and the proper application of the available therapy is imperative to control and reduce the burden of TB.

References

[1] Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: strategies to beat multidrug-resistant tuberculosis. *Sci*. 2002 Mar 15;295(5562):2042-6.

[2] Beresford B, Sadoff JC. Update on research and development pipeline: tuberculosis vaccines. Clinical Infectious Diseases. 2010 May 15;50(Supplement_3):S178-83. https://doi.org/10.1086/651489

[3] World Health Organization. Global tuberculosis control: WHO report 2011. InGlobal tuberculosis control: WHO report 2011 2011.

[4] World Health Organization. Global tuberculosis report 2013. World Health Organization; 2013.

[5] World Health Organization Global tuberculosis Report. Avenue Appia, 1211, 2014, Geneva27, Switzerland.

[6] Lee KW, Lee JM, Jung KS. Characterization of pncA mutations of pyrazinamide-resistant Mycobacterium tuberculosis in Korea. *J Korean Med Sci.*, 2001, 16(5):537-43.

[7] World Health Organization. Global tuberculosis control: WHO report 2011. InGlobal tuberculosis control: WHO report 2011 2011.

[8] Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res*. 2004;120(4):316-353.

[9] Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. *Am Fam Physician.* 2005;72(9):1761-1768.

[10] Doetsch RN. Benjamin Marten and his" New Theory of Consumptions". Microbiological reviews. 1978 Sep;42(3):521.

[11] Daniel TM. Robert Koch and the pathogenesis of tuberculosis [Founders of Our Knowledge]. *Int J Tuber Lung Dis.* 2005 Nov 1;9(11):1181-2.

[12] Daniel TM, Bates JH, Downes KA. History of tuberculosis. *Tuberculosis: Pathogenesis, Protection, and Control*. 1994 May 16:13-24. https://doi.org/10.1128/9781555818357.ch2

[13] Schlossberg DL. Tuberculosis and nontuberculous mycobacterial infections. John Wiley & Sons; 2020 Jul 10.

[14] Dannenberg Jr AM. Pathogenesis of Human Pulmonary Tuberculosis: Insights from the Rabbit Model. ASM Press; 2006.

[15] David HL, Jahan MT, Jumin A, et al. Numerical taxonomy analysis of Mycobacterium africanum. *Int J Syst Evol Microbiol*. 1978 Oct 1;28(4):464-72. https://doi.org/10.1099/00207713-28-4-464

[16] Niemann S, Richter E, Rüsch-Gerdes S. Differentiation among Members of the Mycobacterium tuberculosis Complex by Molecular and Biochemical Features: Evidence for Two Pyrazinamide-Susceptible Subtypes of M. bovis. *J clin microbiol*. 2000 Jan 1;38(1):152-7.

[17] Rivero A, Márquez M, Santos J, et al. High rate of tuberculosis reinfection during a nosocomial outbreak of multidrug-resistant tuberculosis caused by Mycobacterium bovis strain B. *Clin Infect Dis*. 2001 Jan 1;32(1):159-61. https://doi.org/10.1086/317547

[18] Van Soolingen D, Hoogenboezem T, De Haas PE, et al. A novel pathogenic taxon of the Mycobacterium tuberculosis complex,

Canetti: characterization of an exceptional isolate from Africa. *Int J Syst Evolut Microbiol.* 1997 Oct 1;47(4):1236-45.

[19] Delogu G, Fadda G. The quest for a new vaccine against tuberculosis. *J of Infect in Developing Countries*. 2009;3(1):5-15.

[20] Krauss H, Schiefer HG, Weber A. Infectious Diseases Transmissible from Animals to Humans, 3rd ed. 2003;Washington D.C. USA.

[21] Science Photo Library. www.sciencephoto.com.

[22] Brosch R, Gordon SV, Marmiesse M, et al. A new evolutionary scenario for the Mycobacterium tuberculosis complex. *Proceed Nation Acad Sci.* 2002 Mar 19;99(6):3684-9. https://doi.org/10.1073/pnas.052548299

[23] Frieden TR, Sterling TR, Munsiff SS. et al. Tuberculosis. *Lancet*. 2003;362:887-99.

[24] Brennan PJ. Structure of mycobacteria: recent developments in defining cell wall carbohydrates and proteins. *Rev Infect Dis*. 1989 Mar 1;11(Supplement_2):S420-30. https://doi.org/10.1093/clinids/11.Supplement_2.S420

[25] Segal W. Growth Dynamics of in Vivo and in Vitro Grown Mycobacterial Pathogens. The Mycobacteria. A Sourcebook. Marcel Dekker, Inc., New York, NY. 1984:547-73.

[26] Hybiske K, Stephens RS. Exit strategies of intracellular pathogens. *Nat Rev Microbiol*. 2008 Feb;6(2):99-110.

[27] Meena LS. Survival mechanisms of pathogenic Mycobacterium tuberculosis H37Rv. *FEBS J.* 2010 Jun 1;277(11):2416-27. https://doi.org/10.1111/j.1742-4658.2010.07666.x

[28] Behr MA, Sherman DR. Mycobacterial virulence and specialized secretion: same story, different ending. *Nat Med.* 2007 Mar;13(3):286-7. https://doi.org/10.1016/j.tube.2011.03.007

[29] Hunter RL. Pathology of post primary tuberculosis of the lung: an illustrated critical review. *Tuberculosis*. 2011 Nov 1;91(6):497-509.

[30] Sakula A. Robert Koch: centenary of the discovery of the tubercle bacillus, 1882. *Thorax*. 1982 Apr 1;37(4):246-51. http://dx.doi.org/10.1136/thx.37.4.246

[31] Chadwick MV. *Mycobacteria*. 1982, Wright PSG, London, USA.

[32] Petti CA, Weinstein MP, Carroll KC. Systems for Detection and Identification of Bacteria and Yeasts. Manual of Clinical Microbiology, 10th ed. 2011 Jan 1:15-26.

[33] Ouellet H, Johnston JB, de Montellano PR. Cholesterol catabolism as a therapeutic target in Mycobacterium tuberculosis. *Trends Microbiol*. 2011 Nov 1;19(11):530-9. https://doi.org/10.1016/j.tim.2011.07.009

[34] Rutala WA. APIC guideline for selection and use of disinfectants. *Am J Infect Control*. 1990 Apr 1;18(2):99-117.

[35] Dorhoi A, Reece ST, Kaufmann SH. For better or for worse: the immune response against Mycobacterium tuberculosis balances pathology and protection. *Immunological Rev*. 2011 Mar;240(1):235-51. https://doi.org/10.1111/j.1600065X.2010.00994.x

[36] Glickman MS, Jacobs WR. Microbial pathogenesis of Mycobacterium tuberculosis: dawn of a discipline. *Cell*. 2001 Feb 23;104(4):477-85.

[37] Chan J, Fan XD, Hunter SW, et al. Lipoarabinomannan, a possible virulence factor involved in persistence of Mycobacterium tuberculosis within macrophages. *Infection Immunity*. 1991 May 1;59(5):1755-61.

[38] Schlesinger LS, Kaufman TM, Iyer S, et al. Differences in mannose receptor-mediated uptake of lipoarabinomannan from virulent and attenuated strains of Mycobacterium tuberculosis by human macrophages. *J Immunol*. 1996 Nov 15;157(10):4568-75.

[39] Stear MJ. OIE manual of diagnostic tests and vaccines for terrestrial animals. *Parasitol*. 2005 Jun;130(6):727-.

[40] Sreevatsan S, Pan XI, Stockbauer KE, et al. Restricted structural gene polymorphism in the Mycobacterium tuberculosis complex indicates evolutionarily recent global dissemination. *Proceed Nat Acad Sci*. 1997 Sep 2;94(18):9869-74.

[41] Fleischmann RD, Alland D, Eisen JA, et al. Whole-genome comparison of Mycobacterium tuberculosis clinical and laboratory strains. *J Bacteriol*. 2002 Oct 1;184(19):5479-90.

[42] Baril L, Caumes E, Truffot-Pernot C, et al. Tuberculosis caused by Mycobacterium africanum associated with involvement of the upper and lower respiratory tract, skin, and mucosa. *Clin Infect Dis*. 1995 Sep 1;21(3):653-5. https://doi.org/10.1093/clinids/21.3.653

[43] Meyer CG, Scarisbrick G, Niemann S, et al. Pulmonary tuberculosis: virulence of Mycobacterium africanum and relevance in HIV co-infection. *Tuberculosis*. 2008 Sep 1;88(5):482-9. https://doi.org/10.1016/j.tube.2008.05.004

[44] David HL, Jahan MT, Jumin A, et al. Numerical taxonomy analysis of Mycobacterium africanum. *Int J Syst Evolut Microbio*l. 1978 Oct 1;28(4):464-72. https://doi.org/10.1099/00207713-28-4-464

[45] De Jong BC, Antonio M, Gagneux S. Mycobacterium africanum—review of an important cause of human tuberculosis in West Africa. *PLoS Negl Trop Dis*. 2010 Sep 28;4(9):e744. https://doi.org/10.1371/journal.pntd.0000744

[46] Cole ST, Eiglmeier K, Parkhill J, et al. Massive gene decay in the leprosy bacillus. *Nat*. 2001 Feb;409(6823):1007-11.

[47] Browne SG. Some aspects of the history of leprosy: the leprosie of yesterday. *Proc R Soc Med*. 1975;68(8):485-493.

[48] Sansonetti P, Lagrange PH. The immunology of leprosy: speculations on the leprosy spectrum. *Rev Infect Dis.* 1981;3(3):422-69.

[49] Martinez TS, Figueira MM, Cost AV,et al. Oral mucosa as a source of Mycobacterium leprae infection and transmission, and implications of bacterial DNA detection and the immunological status. *Clin Microbiol and Infect*. 2011;17(11):1653-1658.

[50] Beyene D, Aseffa A, Harboe M, et al. Nasal carriage of Mycobacterium leprae DNA in healthy individuals in Lega Robi village, Ethiopia. *Epidemiol Infect*. 2003 Oct;131(2):841-8.

[51] Desikan KV, Sreevatsa. Extended studies on the viability of Mycobacterium leprae outside the human body. *Leprosy Rev.* 1995;66(4):287-295.

[52] Van Beers SM, de Wit MY, Klatser PR. The epidemiology of Mycobacterium leprae: recent insight. *FEMS Microbiol Lett*. 1996 Mar 1;136(3):221-30. https://doi.org/10.1111/j.1574-6968.1996.tb08053.x

[53] Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tuberc Lung Dis.* 2006;10(8):829-837.

[54] Eker B, Ortmann J, Migliori GB, et al. Multidrug-and extensively drug-resistant tuberculosis, Germany. *Emerg Infect Dis*. 2008 Nov;14(11):1700.

[55] Wehrli W, Knüsel F, Schmid K, et al. Interaction of rifamycin with bacterial RNA polymerase. *Proceedings of the National Academy of Sciences of the United States of America*. 1968 Oct;61(2):667.

[56] Dooley SW, Jarvis WR, Martine WJ, et al. MDR Tuberculosis (editorial). *Ann Intern Med*, 1992;117(3):257-258.

[57] Edlin BR, Tokers JI, Greeko MH, et al. An outbreak of multidrug resistant tuberculosis among hospitalized patients with the Acquired Immuno-Deficiency syndrome. *N Engl J Med.* 1992;326(23):1514-1521.

[58] Pearson ML, Jareb JA, Freiden TR. Nosocomial transmission of multidrug resistant tuberculosis-a risk to patients and health care workers. *Ann Intern Med*. 1992;117(3):191-196.

[59] Faustini A. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. *Thorax*;2006:61(2), 158-163.

[60] Telenti A. Genetics of drug resistant Tuberculosis. *Thorax.* 1998;53(9):793-797.

[61] Miller MA, Thibert L, Desjardins F, et al. Testing of susceptibility of Mycobacterium tuberculosis to pyrazinamide: comparison of Bactec method with pyrazinamidase assay. *J Clin Microbiol.* 1995;33(9):2468-70.

[62] Somoskovi A, Parsons LM, Salfinger M. The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in Mycobacterium tuberculosis. *Respiratory Res*. 2001 Jun;2(3):1-5.

[63] CDC. Initial therapy for Tuberculousis in the era of MDR. Recommendations of the advisory council for the elimination of tuberculousis. *MMWR Recomm. Rep.* 1993;42(7):1-8.

[64] Zimhony O, Vilcheze C, Jacobs WR Jr. Characterization of Mycobacterium smegmatis expressing the Mycobacterium tuberculosis fatty acid synthase I (fas1) gene. *J Bacteriol*. 2004;186(13):4051-4055.

[65] Scorpio A, Lindholm-Levy P, Heifets Let al. Characterization of pncA mutations in pyrazinamide-resistant Mycobacterium tuberculosis. *Antimicrobial Agents and Chemotherapy*. 1997 Mar 1;41(3):540-3.

[66] Scorpio A, Zhang Y. Mutations in pncA, a gene encoding pyrazinamidase/nicotinamidase, cause resistance to the antituberculous drug pyrazinamide in tubercle bacillus. *Nat Med*. 1996 Jun;2(6):662-7.

[67] Mdluli K, Slayden RA, Zhu Y, et al. Inhibition of a Mycobacterium tuberculosis beta-ketoacyl ACP synthase by isoniazid. *Sci.* 1998;280(5369):1607-1610.

[68] Shi W, Zhang X, Jiang X, et al. Pyrazinamide inhibits trans-translation in Mycobacterium tuberculosis. *Sci.* 2011;333(6049):1630-1632.

[69] Chang KC, Leung CC, Yew WW, et al. Pyrazinamide may improve fluoroquinolone-based treatment of multidrug-resistant tuberculosis. *Antimicrob Agents Chemother.* 2012;56(11):5465-5475.

[70] Zhang Y, Mitchison D. The curious characteristics of pyrazinamide: a review. *Int J Tuberc Lung Dis*. 2003;7(1):6-21.

[71] Shah N, Wright A, Bai G, et al. Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg Infect Dis*. 2007;13(3):380-387.

[72] World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and

response. Report no. WHO/HTM/TB/2010.3. 2010, Geneva: The Organization.

[73] Sotgiu G, Ferrara G, Matteelli A, et al. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Respir J.* 2009;33(4):871-881.

[74] Calver AD, Falmer AA, Murray M, et al. Emergence of increased resistance and extensively drug-resistant tuberculosis despite treatment adherence, South Africa. *Emerg Infect Dis.* 2010;16(2):264-271.

[75] Cox HS, Sibilia K, Feuerriegel S, et al. Emergence of extensively drug resistance during treatment for multidrug-resistant tuberculosis. *N Engl J Med*. 2008;359(22):2398-2400.

[76] Grange JM, Stanford JL. Dogma and innovation in the global control of tuberculosis: discussion paper. *J R Soc Med*. 1994;87(5):272-275.

[77] Rook GA, Hernandez-Pando R. The Pathogenesis of Tuberculosis. *Annual Rev Microbiol*. 1996;50:259-284.

[78] Sterling TR, Bethel J, Goldberg S, et al. The Scope andImpact of Treatment of Latent Tuberculosis Infection in the United States and Canada. *Am J of Resp Critical Care Med*. 2006;173(8):927-931. https://doi.org/10.1164/rccm.200510-1563OC

[79] Campbell IA, Bah-Sow O. Pulmonary tuberculosis: diagnosis and treatment. *British Med J*, 2006;332(7551):1194-1197.

[80] World Health Organization, Stop TB Initiative (World Health Organization). Treatment of tuberculosis: guidelines. WHO;2010.

[81] Ruiz-Manzano J, Blanquer R, Calpe JL, et al. Diagnosis and Treatment of Tuberculosis. *Arch Bronconeumol*. 2008;44(10):551-566.

[82] Flynn JL, Chan J. Immunology of Tuberculousis. *Annual Rev Immunol.* 2001;19:93-129.

[83] Ulrichs T, Kaufmann SH. New insights into the function of granulomas in human tuberculosis. *J Pathol.* 2006;208(2):261–269.