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# Anti-Microbial Resistance as Multiple Drug Resistance in Tuberculosis

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**ABSTRACT:** Tuberculosis (TB) remains a major global health challenge despite being preventable and curable<sup>1</sup>. One of the difficulties stems from the resilience of its causative bacterium, *Mycobacterium tuberculosis*, which can survive in latent states and develop resistance to existing drugs<sup>6</sup>. This review highlights two interconnected themes in modern TB research: (i) the identification of new molecular targets in the bacterium, and (ii) the development of chemical probes to validate and explore those targets<sup>13, 18</sup>.

Firstly, researchers describe how the TB bacterium's unique cell wall, its energy metabolism (especially the electron transport chain and ATP synthase), and other cellular systems (such as iron uptake and DNA-related enzymes) provide promising avenues for intervention<sup>14, 18</sup>. Many current therapies target only a small fraction of bacterial proteins, and new efforts aim to disrupt vital bacterial functions that have so far been under-exploited<sup>31</sup>. Secondly, advanced chemical biology tools—such as activity-based probes and affinity-based probes—are being used to map bacterial enzymes, to discover which proteins are active in different physiological states (including dormant forms), and to identify biomarkers and medicalizable targets<sup>12, 27</sup>. These tools allow scientists to move beyond simply screening for bacterial kill-rates, instead probing how bacteria survive and resist therapy<sup>3, 23</sup>.

The ongoing challenges posed by tuberculosis highlight the urgent need for innovative approaches in understanding and treating *Mycobacterium tuberculosis*<sup>8</sup>. Traditional therapies target only a limited number of bacterial pathways, leaving significant gaps in the fight against latent and drug-resistant TB<sup>34</sup>. The interaction of new molecular target identification with advanced chemical probe technologies represents a promising shift in TB research<sup>13, 30</sup>. These strategies not only reveal previously unexplored vulnerabilities within the bacterium but also deepen our understanding of its survival mechanisms<sup>12, 23</sup>. By combining precise target discovery with modern validation tools, researchers are paving the way for more effective, shorter-duration, and resistance-proof treatments<sup>9, 30</sup>. Such advancements hold strong potential to transform global TB management and improve patient outcomes<sup>1, 34</sup>.

**KEYWORDS:** Tuberculosis, multidrug resistance, anti-microbial resistance, DOT's, Acquired resistance.

## I. INTRODUCTION

The causative organism of tuberculosis also known as TB is *Mycobacterium tuberculosis* or *M. tuberculosis*. Tuberculosis is one of the major causes of illness and death worldwide<sup>1, 31</sup>. *M. tuberculosis* belongs to the family *Mycobacteriaceae*. It has a very slow growth rate and is peculiar due to its cell wall structure<sup>14, 18</sup>. The microbes of tuberculosis are usually airborne and spread from one person to another. It does not only affect the lungs; it also affects the chest, brain, and other parts of the body. Thankfully, tuberculosis is curable in most cases, but if it is left behind or not subjected to treatment, this tuberculosis can lead to death<sup>31</sup>. When a person develops TB in the throat or lungs, then it might be inhaled by the persons in his surroundings if he/she coughs, sneezes, speaks, or sings.

*M. tuberculosis* is an acid-fast bacillus; hence, it can be differentiated under the Ziehl-Neelsen staining due to its cell wall, which has a high content of lipids, mainly mycolic acids<sup>14</sup>. The complex cell wall makes the bacterium resistant to drying off, detergents, and antibiotics<sup>18</sup>. Therefore, treatment of the disease is difficult<sup>6, 8</sup>.

The *M. tuberculosis* genome size is about 4.4 megabases and codes for various factors, which help this organism to survive within the macrophages of the host<sup>23</sup>. A stashing system of exo-1 targeted to interfere with the membranes and a metabolic pathway of lipids taken from the host to use their fatty acids<sup>18</sup>. In addition, *M. tuberculosis* has developed a DosR-regulated dormancy program that allows it to persist in an inactive state within the host for long periods<sup>12</sup>. This

persistence ability is an important feature for latent tuberculosis infection known as LTBI. LTBI is the biggest problem for eradication efforts<sup>31</sup>. TB bacteria that resist the action of certain medications are described as pre- extensively drug-resistant tuberculosis<sup>2</sup>. Such medicines include vitamin, isoniazid, and others. Since isoniazid and other first-line drugs are very effective against TB bacteria, lack of proper medications leads to multi-drug resistant tuberculosis abbreviated as MDR-TB<sup>1,31</sup>. With the beginning of anti- tubercular chemotherapy, there has been an increase in the rate of DR-TB<sup>6</sup>. However, in the past few years, MDR-TB has become a significant concern and a threat to global efforts made for coping with this disease<sup>1,34</sup>. Treating MDR-TB is an arduous, expensive, and complicated process<sup>8</sup>. The challenges in the control of MDR-TB form the basis of this review. Despite many countries working to manage cases with MDR/RR-TB, only about 125,000 out of the approximate 580,000 new cases reported in 2015 had initiated second-line TB treatment<sup>31</sup>. There is no comprehensive information regarding the quality of care these patients received, and those who were not reported. However, recent reports indicate that only about half of the cases involving MDR/RR-TB and a quarter of those with XDR-TB had successful treatment outcomes<sup>2,34</sup>.

In 2022, there were an estimated 410,000 persons (95% uncertainty interval: 370,000–450,000) with multi-drug resistant or extensively drug-resistant tuberculosis MDR/RR-TB<sup>34</sup>. A significantly lower number of these cases started treatment; approximately 175,650 cases were reported in 2022. This number is about two-fifths of the pre- pandemic figure of 181,533 in 2019<sup>34</sup>. Isoniazid resistance, having overall resistance rates of 16% that vary among recently diagnosed and previously treated cases, provides rifampicin-resistant tuberculosis, RR-TB<sup>11</sup>. According to the World Health Organization, tuberculosis remains one of the top 10 causes of death worldwide and represents the leading cause of death due to a single infectious agent, above HIV/AIDS<sup>31</sup>. In 2020, an estimated 10 million people were diagnosed with TB, and 1.4 million deaths were attributed to the disease<sup>31</sup>. These striking numbers prove once again that it is of the utmost importance to undertake effective control measures<sup>1,8</sup>. Over the years, India has seen a gradual increase in the number of MDR-TB cases<sup>1</sup>. However, it is still not possible to arrive at the true extent of MDR-TB due to the lack of an extensive monitoring system and frequent studies<sup>34</sup>. To make up for this lacuna, in India, every tertiary care centre will have its primary and acquired resistance situations estimated as part of the national strategy<sup>31</sup>.

## II. HISTORY

The first effective antituberculosis drug, streptomycin, was discovered in 1944<sup>22</sup>. The newly identified drug was promptly employed for treatment of patients with TB. In many of the individual TB patients, the condition improved after some months on streptomycin only to decline again during further treatment. It was soon realised that this was a result of the emergence of resistant *M. tuberculosis* strains, rendering streptomycin ineffective<sup>6</sup>. To limit the evolution of resistance, the British Medical Research Council pioneered the first combination therapy for the treatment of a disease by using para- amino salicylic acid together with streptomycin for treatment of pulmonary TB<sup>22</sup>. The subsequent years saw the introduction of an array of different antituberculosis drugs. The discovery of rifampicin in 1965 and the subsequent use of the drug in TB treatment was a game changer, allowing dramatically shortened treatment duration from 18 months or more to 9 months<sup>22</sup>. During the 1990s, the current standard 6-month regimen known as Directly Observed Therapy Short Course was introduced by the World Health Organization<sup>8</sup>. This regimen consists of 2 months treatment with isoniazid, rifampicin, ethambutol and pyrazinamide followed by 4 months of isoniazid and rifampicin, and is highly effective for drug-susceptible TB<sup>8,22</sup>.

Historically, TB was considered incurable until the discovery and use of streptomycin (STR) in 1946<sup>22</sup>. In the first ever clinical trial of such compounds, carried out by BMRC in Great Britain (UK), STR proved to be remarkably effective reducing mortality by a great extent and overwhelming resistance in due course appeared towards this drug<sup>6</sup>. In the 1960s, a trial of isoniazid (INH)-para- amino salicylic acid (PAS) was launched, which suggested that care in the home was equally effective and comparable to treatment in a sanatorium or hospital<sup>22</sup>.

However, the greatest major ambassador concerning this collective health risk is the rising problem of drug resistance because the cure costs up to 2 times or more with limited success and involves severe toxin exposure<sup>8,31</sup>. Infections caused by *Mycobacterium tuberculosis* remain a major global health issue<sup>1,31</sup>. Fully susceptible strains of the *Mycobacterium tuberculosis* bacterium can be effectively treated with a combination of four drugs for six months; this will effectively reach cure rates of about 85% when properly followed<sup>8</sup>. However, patient non-compliance and poor drug diffusion consistently contributes considerably to the failure of treatment and the development of resistance against all antibiotics used globally<sup>6,23</sup>. In fact, clinical resistance has formerly been detected among recently authorized anti-tuberculosis drugs bedaquiline (BDQ) and pretomanid (PA824)<sup>9</sup>.

The intrinsic resistance of mycobacteria to a number of antibiotic classes has generally been ascribed to the atypical composition and structure of mycobacterial cell envelopes<sup>14, 18</sup>. In comparison with other gram-positive bacteria, the cell wall of mycobacteria of the *Mycobacterium* species appears to be thicker and more hydrophobic; this is due to the production of a number of differing lipids, such as mycolic acids<sup>14, 18</sup>. A number of studies performed in various mycobacterial species have indicated that the composition of the cell envelope, in addition to a low number of porins, are important factors in the low permeability of the cell envelope to compounds in general<sup>14, 19</sup>. The cell wall is also composed of a number of lipids, which are bound covalently to the peptidoglycan layer through an arabinogalactan<sup>14</sup>. In addition, the cell wall also contains "extractable" immune-reactive glycolipids<sup>18</sup>. The lipid-rich nature of the cell wall makes the cell wall extremely hydrophobic, thus inhibiting the passage of hydrophilic compounds into the cell wall<sup>18, 25</sup>. Small hydrophilic compounds, such as a number of mycobacterial antibiotics, are believed to enter the mycobacterial cell wall only through the porins, which are filled with water<sup>19, 25</sup>. The expression of the porin gene of *Mycobacterium smegmatis* in a heterologous manner in *M. tuberculosis* indeed lowers the MIC of a number of hydrophilic compounds, indicating that porins may also have a role in the diffusion of hydrophilic antibiotic compounds into the mycobacterial cell wall<sup>19</sup>. However, until recently, there have been no reports of porins in the mycobacterial species *M. tuberculosis*<sup>19</sup>. The outer membrane protein CpnT of mycobacteria appears to have a role in nutrient uptake in the mycobacterial species *M. bovis* BCG and *M. tuberculosis* and in mediating susceptibility in *M. bovis* BCG in relation to nitric oxide/antibiotic susceptibility<sup>19</sup>. This protein appears to undergo positive evolutionary pressures in clinical isolates of *M. tuberculosis*, in the sense that there is an excess of non-syn mutations in a gene that codes for the CpnT protein (Rv3903c)<sup>17</sup>. However, a role of CpnT in the susceptibility of hydrophilic antibiotic compounds in mediating susceptibility in the mycobacterial species *M. tuberculosis* needs to be explored in greater detail; in the sense that there are no phenotypically apparent antibiotic-resistant mutations in CpnT in vitro deletion mutants of CpnT in mycobacteria of the species *M. tuberculosis*<sup>17</sup>. However, the studies verify the existence of porins in the outer membrane of *M. tuberculosis*, as well as their involvement in the internalization process of hydrophilic compounds<sup>19</sup>. Moreover, it is proposed that the physical arrangement of lipids within the bacterial cell wall affects the fluidity of the bacterial envelope<sup>27</sup>. Recently, a study evaluated the fluidity of the envelope membranes of live cells of *M. smegmatis*, as well as other actinobacteria, via the measurement of the displacement of fluorescein-tagged trehalose derivatives by mycolyl transferases<sup>27</sup>. They managed to show that, compared with other actinobacteria, the fluidity of *M. smegmatis* membranes is lower<sup>27</sup>. This is attributed to the properties of mycolic acids (size and functional groups)<sup>27</sup>. Moreover, it was found that when treated with sub-inhibitor concentrations of ethambutol, the fluidity of *M. smegmatis*'s envelope membranes, as well as the diffusion of compounds, is increased<sup>27</sup>. This provides hope for potential novel combination treatments, where the fluidity of the envelope membranes is increased by ethambutol, making *M. tuberculosis* susceptible to drugs against which it is naturally resistant<sup>27</sup>.

The unique features of mycobacterial cell envelopes make diffusion of lipophilic molecules like various members of several antibiotic classes, such as macrolides, rifamycin's, tetracyclines, and fluoroquinolones, difficult<sup>18, 25</sup>. Nevertheless, it does appear that diffusion is a function of molecule hydrophobicity, at least in part, with greater ease of diffusion shown for lipophilic molecules in mycobacterial cell envelopes<sup>25, 26</sup>. The notion that mycobacterial cell envelope lipids contribute importantly to inherent resistance of mycobacteria to most hydrophobic antibiotics is supported further by experiments conducted in mutant strains with defects in lipids and reduced growth tolerance with lipophilic drugs that were made sensitive by these mutant strains in drug susceptibility assays using a strain which is naturally resistant to a particular drug<sup>14, 18</sup>. In a most recent venture, diffusion of compounds through the mycobacterial cell wall has been modelled in a specific research context in which lipophilicity, but not lipophilicity alone, has been noted to be important for compounds in mycobacterial permeability<sup>13</sup>.

### III. TYPES OF DRUG-RESISTANT TB

A. Monoresistance – Resistance to only one first-line anti-TB medication. Polydrug resistance: Resistance to more than one first-line anti-tuberculosis drug, but not including resistance to both isoniazid and rifampicin<sup>8, 31</sup>.

B. Pre-XDR TB is a relatively novel term that describes TB which is resistant to rifampicin and isoniazid and either one or both of the following: fluoroquinolones, injectable second-line agents (pre- XDR-TB but not both) <sup>2, 31</sup>. Therefore, under the usual MDR-TB regimen, pre-XDR TB subjects with fluoroquinolones or isoniazid resistance receive fewer effective medicines. It might intensify existing drug resistance even more and speed up the development of extensively drug resistant tuberculosis<sup>2, 34</sup>.

C. Extensively drug-resistant tuberculosis (XDR) is defined as *M. tuberculosis* that is recalcitrant not only to INH and RIF but also to other classes of medications that define the backbone of drug-resistant tuberculosis treatment regimens, a quinolone, and one of the second-line injectable drugs—either kanamycin (KAN), amikacin (AMK), capreomycin (CAP)<sup>2,31</sup>.

D. Multidrug resistance (MDR): Totally drug-resistant TB (TDR-TB) strains have been defined as strains that are completely resistant to all existing anti-TB drugs, although this number and level of resistance has not been defined<sup>2,34</sup>. The presence of these strains has reinforced the medical and public health imperative in managing drug-resistant TB<sup>1,8</sup>.

#### **IV. DRUG RESISTANCE MECHANISM**

TB bacteria have developed various drug resistances<sup>3,6</sup>. When the bacteria produce enzymes that either alter or inactivate the drugs, the drugs become less effective<sup>3,24</sup>. Adjusting drugs involves altering the drug molecule through chemicals. Such alterations will ensure that the drug does not react with its target<sup>3</sup>. Target adjustment involves gene mutations that affect the target location of the drug<sup>4,5</sup>. Such mutations ensure that the drug target is less sensitive to the drug<sup>4,11</sup>. If the target of the drug metabolism is altered by the bacterium, the bacterium is said to have undergone "targeted alteration." There are proteins in bacterial cells that work as pumps to remove drugs<sup>21,23</sup>. The drugs are removed through diffusion in large amounts<sup>21</sup>. The impermeable walls of the TB bacterium also work as drug resisters since the drugs cannot penetrate the walls<sup>14,18</sup>.

##### **4.1. INTRINSIC OR INNATE RESISTANCE MECHANISM**

Intrinsic drug resistance mechanisms account for the capability of *Mycobacterium tuberculosis* to overcome the cytotoxic actions of antibiotics<sup>14,24</sup>. The natural or innate resistance mechanisms of *Mycobacterium tuberculosis* that make the bacterium resistant to drugs can be defined as follows: The intrinsic characteristics of *Mycobacterium tuberculosis* make it difficult for antibiotics to penetrate the bacterial cell walls<sup>14,18</sup>.

1. The cell wall of *Mycobacterium tuberculosis* also has a special lipid structure and proportion<sup>14,18</sup>. Mycolic acids, wax D, and cord factors are its three prominent components. Arabinogalactan is found in its outer mycomembrane and peptidoglycan in the inner membrane of its cell wall<sup>14</sup>. The membrane consists of two sides: the outer side contains lipids like phospholipids, trehalose mycolate, glycopeptide lipids, and lipoglycans; long chain mycolic acids are found in the inner side<sup>14,18</sup>. The cell wall is thick and lipophilic because of a massive amount of its lipid material that prohibits diffusion of some specific antibiotics like rifampicin, macrolides, fluoroquinolones, and tetracyclines<sup>18,25</sup>. Arabinogalactans form a hydrophilic layer and are responsible for its impermeability to water-loving substances<sup>14,19</sup>. Impermeability causes a concentration of antibiotics in the surrounding environment of the cell<sup>18,25</sup>. The various cellular components like enzymes like beta-lactamase are released out of the cells; beta-lactamase degrades beta-lactam antibiotics or loses its effectiveness by transforming to beta-lactamase inactivated or beta-lactamase inactivated form<sup>3,24</sup>. Because of the impermeable nature of the cell walls, drug resistance can be overcome due to the deficiency of enzymes and proteins<sup>14</sup>. *Mycobacterium tuberculosis* possesses intrinsic resistance to the drug Fosfomycin, a murA inhibitor, because it acts as a biosynthetic enzyme for peptidoglycan and covalently interacts with the cysteine residue present at the active site to convert it into aspartic acid<sup>24</sup>. Trehalose dimycolate or TDM is a crucial factor that helps *Mycobacterium tuberculosis* resist the impermeable nature of the cell walls and is synthesized using the protein produced from the Ag85 gene of the antigen<sup>18</sup>. It implies that the mutant of the ag85 gene will affect the susceptibility of *M. tuberculosis* to the starting drugs and the prominent broad-spectrum antibiotics because TDM is a major factor present in the intrinsic resistance<sup>18</sup>. The other layer of the cell wall consists of porins, which are proteins that form pores, making way for the entry of hydrophilic compounds/antibiotics into the cell<sup>19</sup>. Therefore, the reduced number of porins combined with the lipid composition of the cell wall prevents the entry of such hydrophilic compounds<sup>19,25</sup>. The bacteria are sensitive to anti-bacterial compounds due to a protein referred to as CpnT, which is located in the outer membrane of the cell wall<sup>19</sup>. According to Danilchanka et al., *Mycobacterium tuberculosis* with the cpnT mutant is more resistant than others<sup>17</sup>.

2. Certain genes allow *Mycobacterium tuberculosis* to thrive in micro-oxygen environments, and thus most require triglyceride production directly from acetyl CoA<sup>12</sup>. Acetyl CoA is an essential part of the tricarboxylic acid (TCA) cycle, decelerating the metabolism rate<sup>12</sup>. A low generation rate allows the spread of *Mycobacterium tuberculosis*. Their resistance to most antibiotics results from low metabolism and high generation time showed that the stability of

antibiotics such as Carbapenems is shorter than the growth rate of *Mycobacterium tuberculosis*, and thus they do not work on *Mycobacterium tuberculosis*<sup>12,28</sup>.

3. The efflux pump has proteins that space the membranes and are required for bacterial metabolism, physiology, nutrient transport, toxin transport, and water or signalling molecule transport across the bacterial envelope have proved the importance of efflux pumps in *M. tuberculosis* intracellular growth and replication in macrophages<sup>21,23</sup>. Mycobacterial efflux pumps in *M. tuberculosis* have been closely related with the efflux of all antitubercular drugs such as ethambutol, fluoroquinolones, bedaquiline, clofazimine, isoniazid, rifampicin, and streptomycin<sup>21,23</sup>. Upon macrophage infection, mycobacterial efflux pumps are induced; these pumps remain functional even after release of infected cellular products from macrophage and cause multidrug resistance in the macrophage cell<sup>21,23</sup>. Literature survey has shown that chromosomal mutations in most antitubercular drug-resistant *Mycobacteria* strains lead to efflux pump overproduction, thus resulting in efflux of drugs<sup>20,21</sup>. Milano et al. mentioned in their research that *mmpR* mutation leads to efflux pump protein overproduction and confers isoniazid resistance<sup>20</sup>. Have identified the five superfamilies of drug efflux pumps to be: The drug efflux pumps belong to (i) the multidrug and toxic-compound extrusion (MATE) superfamily, (ii) the resistance nodulation cell-division (RND) superfamily, (iii) the small-multidrug resistance (SMR) superfamily, (iv) the major-facilitator superfamily (MFS), and (v) the ATP-binding-cassette (ABC) superfamily<sup>21,23</sup>. The ABC superfamily belongs to the primary ATP-dependent or primary transporter pumps, while the remainder belong to the secondary-transporter proton motive-force-dependent superfamily<sup>21</sup>. The expression of efflux pumps is triggered by antibiotics, which overexpress *jefA*, *drxA*, *drxB*, *efpA*, *mmr*, and *Rv1217-Rv1218* genes upon isoniazid and rifampicin stress, among others<sup>20,21</sup>. The overexpression of the *jefA* gene results in isoniazid, streptomycin, and ethambutol resistance<sup>20</sup>.

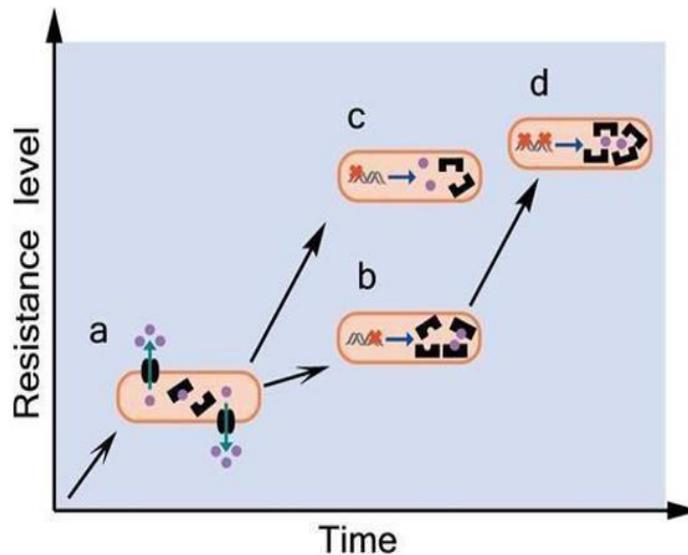
#### 4. Degradation and Modification of Antibiotics

*Mycobacterium tuberculosis* has several enzymes for degrading or inactivating various forms of antibiotics<sup>3,24</sup>. Examples of these enzymes include aminoglycosides,  $\beta$ -lactams, and macrolides. Amongst the antibiotics, beta-lactams have a specific action that entails inhibiting the bacterial enzyme transpeptidase<sup>3</sup>. *Mycobacterium tuberculosis* expresses a beta-lactamase enzyme of Ambler type A classification, termed enzyme *Blac*<sup>3,24</sup>. Antibiotics that undergo modifications through methylation and acetylation cannot interact with their target proteins specifically; hence, they are not active<sup>24</sup>. Modification of antibiotics with special chemical groups makes them inactive<sup>3</sup>. Aminoglycoside modifying enzymes like acetyl transferases are the enzymes that catalyses the acetylation of the 2' amine groups in the aminoglycoside antibiotics<sup>3,24</sup>. Antibiotics that contain aminoglycosides include Neomycin, Ribostamycin, Kanamycin, Gentamycin, and Tobramycin<sup>3</sup>. The product of this gene is a protein that helps in the acetylation of drugs that have the chemical structure of either cyclic peptides or that of aminoglycosides<sup>24</sup>. It is also the most persuasive evidence that *Mycobacterium tuberculosis* inactivates antibiotics<sup>3,24</sup>. It is called the enzymatic modification<sup>3</sup>. This gene product is involved in the inactivation of the second-line aminoglycoside antibiotics (Kanamycin A) through acetylation as well as Cyclic peptide antibiotics (Capreomycin) through acetylation<sup>24</sup>. It is also involved in the inhibition of the immune system of the human body by protecting *Mycobacterium tuberculosis* through the promotion of long lives of the Macrophages<sup>24</sup>.

5. The drugs are selective in their binding capacity<sup>4,11</sup>. Therefore, target modification will inhibit the binding of the drug to a particular target site; this leads to resistance to that particular drug<sup>4</sup>. The drugs inhibit the binding of lincosamides, macrolides, streptomycin, and rifampin to *Mycobacterium tuberculosis* by target modification<sup>4,11</sup>. Additionally, these drugs not only inhibit the translocation of peptidyl-tRNA but also inhibit protein synthesis; these drugs also inhibit the growth of *Mycobacteria* by reversibly binding to a particular site on the 50S subunit of rRNA<sup>4,11</sup>.

6. *Mycobacterium tuberculosis* has a number of distinct systems in place to evade anti-tuberculosis medication, one of which is molecular mimicry<sup>5</sup>. The inhibition of DNA gyrase or topoisomerase by fluoroquinolones prevents DNA replication, transcription, repair, and degradation<sup>5</sup>. This results in cell death. The Mycobacterial fluoroquinolone resistance protein A, also termed *MfpA*, is found in *Mycobacterium tuberculosis* and mimics DNA B-form in terms of size and shape, which enables it to interact with DNA gyrase, obstructing the interaction of fluoroquinolone with DNA gyrase<sup>5</sup>.

#### 4.2 ACQUIRED RESISTANCE



**Fig.1** Levels of drug resistance resulting from various mechanisms

The red cross represents chromosomal mutations. (a) Low-level drug resistance resulting from efflux pump induction. The depiction of efflux pumps is not needed in subsequent stages. (b) Low-level drug resistance resulting from target protein overproduction caused by chromosomal mutations. (c) High-level drug resistance resulting from modification of drug target proteins due to chromosomal mutations. (d) High-level drug resistance resulting from target protein overproduction and modification caused by two independent chromosomal mutation.

Drug resistance is always an outstanding beneficial trait for *M. tuberculosis* to possess within a population since these resistance mechanisms result in acquiring an edge for these new developing mycobacteria compared to their susceptible cell counterparts under constant selective pressures exerted by drug resistance selection<sup>6,24</sup>. The constant drug exposure exerted through their long treatment courses for TB infections by these patients is contributing to strengthened pressures for evolution to offer advantages to their mutated mycobacteria by acquiring resistance to these drugs since these resistant mutants normally have never coexisted with their drug-susceptible cell counterparts to outnumber them because of their lower selective survival rates compared to their drug-susceptible cell counterparts under these constant pressures exerted by drug resistance selection<sup>6</sup>. All these are happening during combined drug therapy for TB infections to make these mycobacteria have undergone steady evolution to possess constant resistance to all available TB drugs over time<sup>6,24</sup>. Furthermore, aside from their constant survival adaptation for their mycobacteria to always acquire advantages over their mycobacteria cell counterparts to supply sufficient prominent pressures for these mycobacteria to have these constant drug resistance advantages to stand out over their mycobacteria cell counterparts over time without posing threats to human health with their constant drug resistance against TB drugs with a scenario under which these mycobacteria are predicted to evolve over time to eventually be anticipating to stand out over their mycobacteria cell counterparts to always increase their prominent advantages over their mycobacteria cell counterparts without posing threats to human health under these constant pressures exerted by their constant drug resistance selection pressures against TB drugs to eventually have these mycobacteria acquiring advantages over their mycobacteria cell counterparts over time without posing threats to human health with their constant drug resistance against TB drugs; their constant exposures to their bactericidal functions through these TB drugs might have produced mediations for their radical-induced mutagenesis to occur<sup>6,24</sup>.

## V. ANTIMICROBIAL RESISTANCE MECHANISM

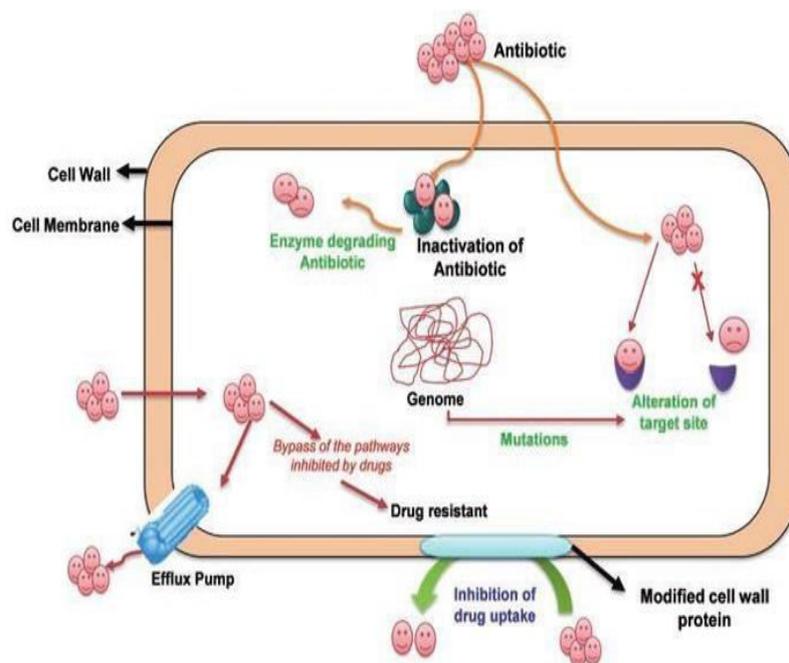


Fig.2 Mechanism of anti-microbial resistance

Unlike other bacterial microorganisms, *M. tuberculosis* attains AMR through three processes, namely, mutations pertaining to activators, target mutations, and efflux pumps<sup>3,21</sup>. Basically, the three processes decrease the permeability of the antimicrobial agents, utilize the *M. tuberculosis* enzymes for the alteration of antimicrobial agents, extrude all antimicrobial agents with the capacity to enter the *M. tuberculosis* envelope through the efflux pump, and change the gene expressions due to the adaptation needed for the antimicrobial agent's reaction<sup>3,21,24</sup>. Furthermore, the envelope cell wall contains four compartments that provide structural support and protection from osmotic change<sup>14,18</sup>. These four compartments include inner plasma membrane, periplasmic space, inner core enfold that comprises peptidoglycan (PG) covalently bonded to arabinogalactan (AG) and mycolic acids (MAs), peripheral lipid layers composed of noncovalently bonded lipids and glycolipids, which include trehalose dimycolate (TDM), phthiocerol dimycocerosates (PDIMs), mannose-capped lipoarabinomannan (ManLAM), sulfolipids (SLs), phosphatidyl-myo-inositol mannosides (PIMs), and phenolic glycolipids (PGLs), and the outermost cell wall compartment that is usually called the "capsule"<sup>14,18</sup>. Moreover, the envelope of *M. tuberculosis* not only provides structural support but is also arguably presented at the frontline during the bacterium-host interaction, where reportedly, many molecules from the outer cell envelope molecules take part in phases of infection with dominant contributions for *Mycobacterium* immunological understanding and AMR developments<sup>14,18</sup>.

Ethambutol, Pyrazinamide, Isoniazid, and Rifampicin are used for treating tuberculosis infections of *Mycobacterium tuberculosis*-type<sup>8</sup>. Ethambutol works by inhibiting cell walls through arabinosyl transferase; Pyrazinamide inhibits energy metabolism; also creates an acidic environment; Isoniazid inhibits mycolic acid synthesis through inhibiting InhA; Rifampicin inhibits transcription through RNA polymerase-binding<sup>4,8,11</sup>. Such drug combinations work efficiently for treating infections; however, these are capable of developing resistance to TB but increase TB resistance instead<sup>6</sup>. Because of differences in health care standards for each individual, there is an increase in drug-resistant *Mycobacterium tuberculosis* cases across the globe; this hinders TB treatment<sup>1,31</sup>. *Mycobacterium tuberculosis* exhibits multiple mechanisms for developing drug resistance; these include cell-wall impermeability; efflux pumps; drug degradation/Modification; target alteration; target mimicry<sup>3,14,21</sup>. All these can be categorized into two types based on mechanisms: innate resistance mechanisms; Acquired Molecular resistance mechanisms<sup>3,24</sup>.

## VI. MULTI-DRUG RESISTANT TUBERCULOSIS

MECHANISM:

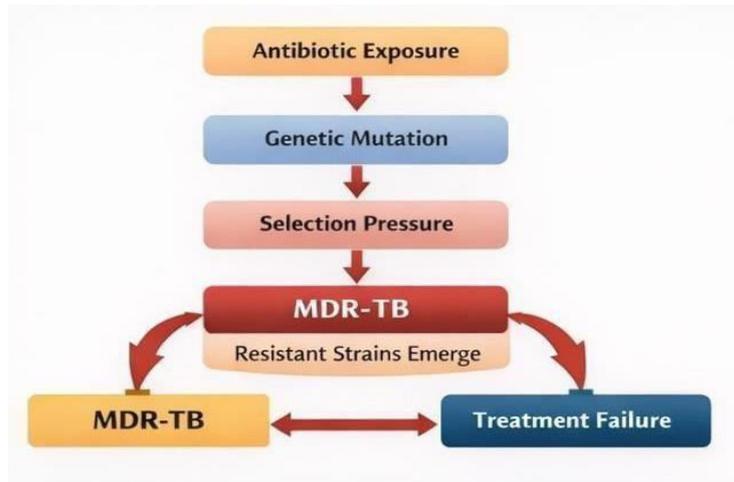
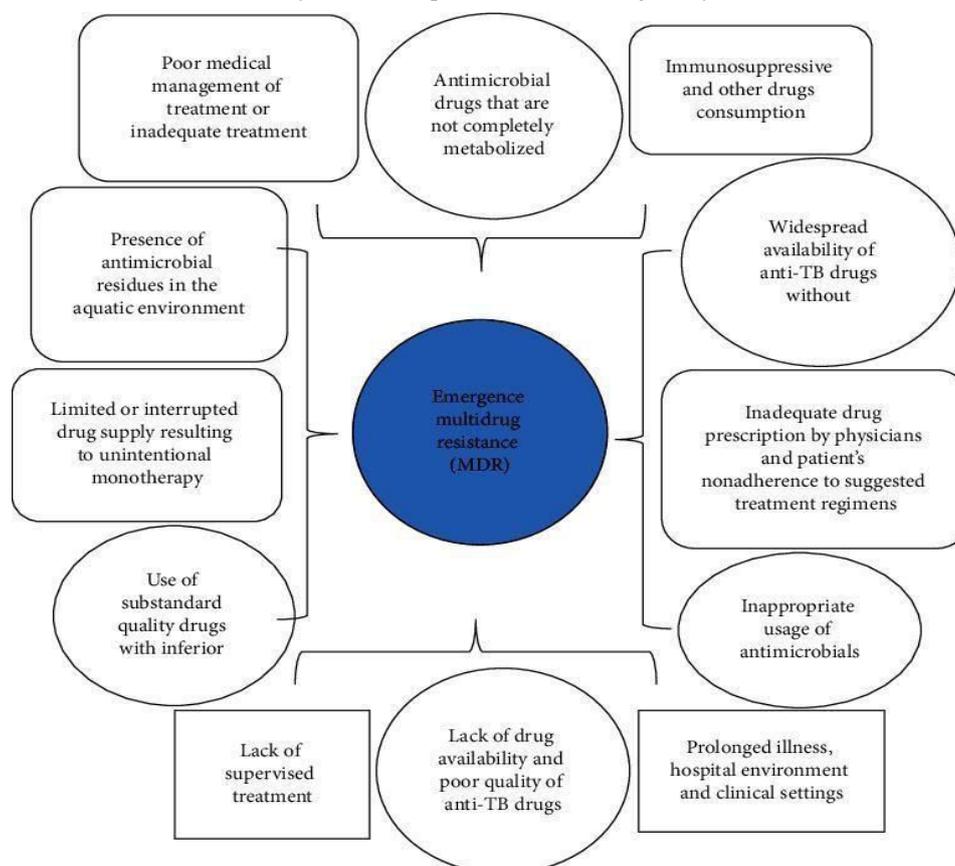


Fig 3: Development of MDR-TB

Multi-Drug Resistant Tuberculosis (MDR-TB) represents a significant challenge in the fight against TB, as it resists at least two of the most potent first-line anti-TB medications, isoniazid and rifampicin<sup>1,8</sup>. Isoniazid is a prodrug that, when metabolized by the mycobacterium's catalase-peroxidase enzyme KatG, becomes active as isonicotinoyl-NAD and disrupts essential steps in the synthesis of mycolic acids<sup>11</sup>. This inhibition disrupts cell wall integrity and generates reactive oxygen species (ROS), contributing to INH's high bactericidal activity, particularly in the first two days of treatment<sup>11</sup>. However, *M. tuberculosis* can develop INH tolerance, reducing its effectiveness over time<sup>12</sup>.

The primary mechanisms of INH resistance include genetic mutations and metabolic adaptations<sup>11,12</sup>. Mutations in the *katG* gene reduce the enzyme's ability to convert INH to its active form, while mutations in the *inhA* promoter led to overexpression of the target enzyme, requiring higher drug concentrations for inhibition<sup>11</sup>. MDR-TB is mainly due to inadequate or suboptimal treatment of TB where the selection for resistant strains takes place<sup>6,8</sup>. This includes scenarios where patients do not adhere to their prescribed treatment regimens, healthcare providers prescribe incorrect treatments, or there is a lack of access to quality-assured drugs<sup>8,31</sup>. As a result, the treatment of MDR-TB requires combination of second-line drugs and prolonged treatment<sup>8</sup>. This TB infection not only poses a threat to individual patients but also to public health, as these resistant strains can spread to others<sup>1,31</sup>. Effectively addressing MDR-TB requires a comprehensive approach, incorporating second-line therapies, which are associated with more severe side effects and extended treatment timelines<sup>8,34</sup>. Moreover, preventing the spread of MDR-TB demands robust public health measures, including rapid and accurate diagnostic capabilities, effective patient management, and ensuring the availability and correct administration of anti-TB medications<sup>8,31</sup>.



**Fig 4: Reasons for MDR-TB**

The main mechanisms of MDR are given by:

- a. Drug Efflux Pumps – Cells overexpress membrane transporters (such as P-glycoprotein and ABC transporters) with active efflux of drugs from the cell, thus decreasing intracellular drug concentrations below therapeutic levels<sup>21,23</sup>.
- b. Increased Drug Uptake (Increased Permeability) – Changes in the cell membrane/cell wall result in a decrease in drug uptake, causing a decrease in drug accumulation<sup>14,18</sup>.
- c. Drug Inactivation or Modification – Enzymes produced by cells work to chemically alter or break down drugs, rendering them ineffective (e.g.,  $\beta$ -lactamases produced by bacterial cells)<sup>3,24</sup>.
- d. Change in Drug Target – The structural changes or mutations in the drug's target site result in decreased drug-binding affinity and thereby reduced drug effectiveness<sup>4,11</sup>.
- e. Overproduction of Drug Target – As the synthesis level of the targeted molecule increases, it reduces the effect of the drug, and as such, the concentration needed for inhibition increases<sup>4,12</sup>.
- f. Bypass of Metabolic Pathway – Cells evolve by-pass pathways in their metabolism that avoid or circumvent the drug-inhibited step in order for survival<sup>12,24</sup>.
- g. Improved DNA Repair Mechanisms – Enhanced DNA repair mechanisms undo the effects of chemotherapeutic or antimicrobial agents<sup>5,24</sup>.
- h. Biofilm Formation in Microorganisms – The microbial cells contained within biofilms also resist drug penetration and change their metabolic conditions, making them multidrug-resistant<sup>28</sup>.

## VII. ONGOING TRIALS

Levofloxacin (Lfx), which is used for treating MDR-TB contacts, has been proven to be affordable, feasible, and acceptable to HCWs<sup>8</sup>. This particular drug does not demonstrate any relevant interactions with highly active antiretroviral agents. It will be assumed that acceptability levels are going to be relatively high in consideration of the seriousness of MDR-TB<sup>8</sup>. Although it represents a giant leap forward, the application of quinolone agents for the

preventive treatment of MDR-TB contacts is still not the final answer<sup>5,8</sup>. There are many Mycobacteria tuberculosis isolates resistant to quinolone agents (pre-XDR TB)<sup>2,5</sup>. According to the WHO estimates in 2023, 19% of the total population of MDR/RR in the world had shown resistance to quinolone agents<sup>34</sup>. Also, in Europe, the distribution of pre-XDR isolates is even more worrisome, at 26.9% within the European Union by 2022 and 35.2% in non-EU states<sup>34</sup>. Secondly, the incidence of adverse events caused by quinolone agents within the adult population is considerable<sup>8</sup>. It can be an obstacle to the strategy's immediate application in a country. In this sense, other techniques should be the object of study<sup>8,30</sup>.

Novel phase III trials have now commenced to assess a variety of regimens for TPT among MDR-TB cases<sup>9</sup>. The PHOENIX-MDR TB (NCT03568383) clinical trial sought to evaluate the safety and efficacy of a delamanid regimen for a period of 6 months compared to a regimen of isoniazid for a 6-month course in high-risk household contacts of adults with MDR-TB in a follow-up period of 96 weeks<sup>9</sup>. This open-label clinical trial includes adults and children but excludes women who become pregnant at the time the research participants are recruited. This research will reassess the effects on those who become pregnant when using delamanid<sup>9</sup>. The expected completion date for these clinical trials is in 2027<sup>9</sup>. BREACH-TB [NCT0656848] represents a larger clinical trial which also considered MDR-TB contacts<sup>9</sup>. It is an unblinded, multicenter, randomized clinical trial which is soon to begin recruiting in March 2025. It aims to evaluate the efficacy and safety of BDQ compared to the WHO recommended regimens in the prevention of TB disease for 96 weeks<sup>9</sup>. It considers PLWH, as well as family contacts of persons with drug-susceptible TB and MDR-TB patients<sup>9</sup>. The control in the first two groups will be 1 month of daily isoniazid and rifapentine or 3 months of weekly isoniazid and rifapentine<sup>9</sup>. For the others, 6Lfx control will be observed in recently contacted people among DR-TB infectious cases<sup>8,9</sup>.

## VIII. DIAGNOSIS OF RESISTANCE TO ANTI-TUBERCULOSIS MEDICATIONS

In vitro methods of diagnosis of resistance to anti-TB drugs may be categorized into phenotypic tests, which depend on culture growth under anti-TB drugs, and genotypic tests, which include identification of the presence of mutations leading to resistance<sup>7,16</sup>.

### 8.1 PHENOTYPIC METHODS

Phenotypic susceptibility testing, also known as drug susceptibility testing, is done in solid media or liquid media<sup>16</sup>. The susceptibility tests done in solid media culture, which are Lowenstein-Jensen and Ogawa-Kudoh, involve the following methods: (a) Proportion Method, (b) Absolute Concentration Method, and (c) Resistance Ratio Method<sup>16</sup>. The traditional Proportion Method is considered to be most widely used globally and in Brazil<sup>16</sup>. One drawback of the susceptibility tests done in solid media is that they take a period of two months to produce results<sup>16</sup>.

Liquid medium, employing the BACTEC MGIT 960 system, shortens the time needed for the detection of *M. tuberculosis* to two weeks, and thereafter, within 1-2 weeks, the sensitivity test result is obtained<sup>16</sup>. The sensitivity and specificity of the MGIT 960 system (96% and 94.6%, respectively) are comparable to those of the proportion method, and the sensitivity test has already been proved valid in Brazil<sup>16</sup>. The major drawback of the sensitivity test using liquid medium is its high cost<sup>16</sup>. The sensitivity of susceptibility testing depends on the drug, and the sensitivity of testing is higher in rifampicin and isoniazid compared to ethambutol and streptomycin<sup>16</sup>.

### 8.2 GENOTYPIC METHODS

Genotypic techniques, also known as molecular techniques, rely on the detection of the mutations responsible for resistance to anti-tubercular drugs<sup>7,16</sup>. Many genotypic techniques have been developed recently due to the need to determine resistance to anti-tubercular drugs quickly<sup>7,16</sup>. Currently, the most frequently utilized molecular techniques are the Genotype MTBDRplus, the INNO- LiPA Rif.TB, and the Xpert MTB/RIF<sup>16</sup>. Genotype MTBDR plus, developed by Hain Life science, detects mutation in the *katG*, *inhA*, and *rpoB* genes, estimating resistance categories of R and H<sup>16</sup>. Sensitivity and specificity of the test for the estimation of R-resistance are 98% and 99% respectively, and for the estimation of H-resistance, the sensitivity is 85% and the specificity is 99%<sup>16</sup>. INNO- LiPA Rif.TB, having a sensitivity of 97% and a specificity of 99% respectively, estimates R-resistance by identifying the mutation in the *rpoB* gene<sup>16</sup>. Y. Z. Li et al. finally describe the Xpert MTB/RIF, where R-resistance can be identified within a couple of hours, with no need for a sophisticated lab setup, allowing the test to be done at the treating institution itself, meaning at the place where the patient is being treated<sup>16</sup>. Sensitivity for the diagnosis of TB by the Xpert MTB/RIF test has been found to be 70% to 100% for a positive culture, and 60% when the patient has TB but the cultures are

negative<sup>16</sup>. Specificity varies from 91% to 100% respectively<sup>16</sup>. For R-resistance, the sensitivity is 98% and the Specificity is 99% respectively<sup>16</sup>.

Although it has been underscored that the perspective of using molecular tests, also known as rapid molecular tests, has been promising for resistance diagnosis, it has been warned that these tests should be validated in countries in which they will be used, based on the diversity of mutation frequency according to the region<sup>7,16</sup>. In this sense, it has been initiated in Brazil the validation process of these tests of a quick diagnosis of resistance<sup>7,16</sup>.

## **IX. TREATMENT OF MDR-TB**

The treatment of MDR-TB is expensive and complicated, given that second-line drugs are necessary, which are also shown to have an increased incidence of side effects<sup>8,34</sup>. Moreover, it also requires a longer treatment period than when using the drug regimen for the first time<sup>8</sup>. The cumulative findings on the outcome of MDR-TB treatment are still very fragile and have only been reported on the basis of observations<sup>8,34</sup>. The lack of standardization with respect to the choice of drug regimens (treatment periods, whether supervised or self-administered) is definitely an important drawback in evaluating different studies<sup>8</sup>. However, certain literature reports have suggested that service provision within the health sector, along with supervised administration of the drug, are factors that help in improving success rates<sup>8,31</sup>. Moreover, certain mathematical studies have also suggested that this can be cost-effective even in countries with scarce economic resources<sup>8,31</sup>. Resistant TB, especially in MDR-TB and XDR-TB, constitutes a significant challenge, which has to be met<sup>2,8</sup>. There should be efforts towards improved management of the disease, especially looking for new drugs, which will ensure a shorter treatment period can be adopted for MDR-TB and XDR-TB<sup>9,30</sup>. Optimal therapy for MDR-TB, considered as that resistant simultaneously to R and H (and with or without resistance to other first-line drugs), therefore is a problem that needs to be addressed within the framework of present knowledge<sup>8,34</sup>. Primarily, the following difficulties would be posed: the high cost of therapy, the low effectiveness rate, the adverse reactions that the drugs would cause, and the long therapeutic time<sup>8,34</sup>. It was found that in the latest meta-analysis conducted with the objective of comparing the results of retrospective cohort studies on the treatment outcomes for patients with MDR-TB that the average rate for success is 69%, and moreover that supervised therapy for at least 18 months is more effective<sup>8,34</sup>. Certain principles must be followed for an appropriate treatment regimen to be planned for MDR-TB<sup>8</sup>:

- (1) co-administration of at least four proven anti-myco-bacterially active drugs, of which three must have never been administered before;
- (2) inclusion of an anti-TB fluoroquinolone agent (ofloxacin, levofloxacin, and/or moxifloxacin);
- (3) inclusion of an injectable anti-TB agent (streptomycin, amikacin, kanamycin, and/or capreomycin);
- (4) extensive and supervised treatment over 18 to 24 months with experienced teams at tertiary referral institutions<sup>8</sup>.

### **DOTS (Directly Observed Treatment)**

DOTS-Plus, a community-based treatment strategy that specializes in MDR-TB care by means of the widely recognized and utilized initiative, Directly Observed Therapy – Short Course (DOTS), has been a considerable success globally<sup>8,15</sup>. In these settings, this strategy has been identified as a suitable means for effectively treating poor rural locations suffering from the presence of MDR-TB<sup>8,15</sup>. Lima, Peru, has been one of the successful sites for this treatment strategy that ensures a cure rate above 80%<sup>8</sup>.

However, TB care professionals have focused on the introduction of the DOTS strategy to the Republic of Georgia, since it is a guidelines-based program with a passive case-finding orientation<sup>15</sup>. This means that the approach relies on voluntarily approaching healthcare professionals by the clients, as opposed to mandatory screenings<sup>15</sup>. As medical anthropologists Erin Koch, among others, have argued, the healthcare approach might not be appropriate in all cultures<sup>15</sup>. Therefore, the DOTS strategy always needs to be transformed regarding the practices and the everyday life of each particular culture<sup>15</sup>. Erin Koch applies the view of "structural" violence developed by Paul Farmer: "a perspective on how institutions, environment, poverty, and power reproduce, solidify, and naturalize the uneven distribution of disease and access to resources"<sup>10,15</sup>. She is currently examining the efficacy of the DOTS strategy for the pervasive illness of tuberculosis within the Georgian prison population<sup>15</sup>. Whereas within the country the DOTS passive case finding method has been successful among the population at large, the multi-level surveillance within the prison system appears more effective in preventing the diffusion of the disease, as well as achieving a higher rate of cure<sup>15</sup>. Koch points out critically that since the DOTS strategy is meant for behavior change on the part of the

individual without modification of the necessity for change for the institutional, political, and economic context, certain drawbacks occur, including MDR tuberculosis<sup>15</sup>.

## X. CHALLENGES RELATED TO ANTIMICROBIAL RESISTANCE IN MULTIDRUG- RESISTANT TUBERCULOSIS

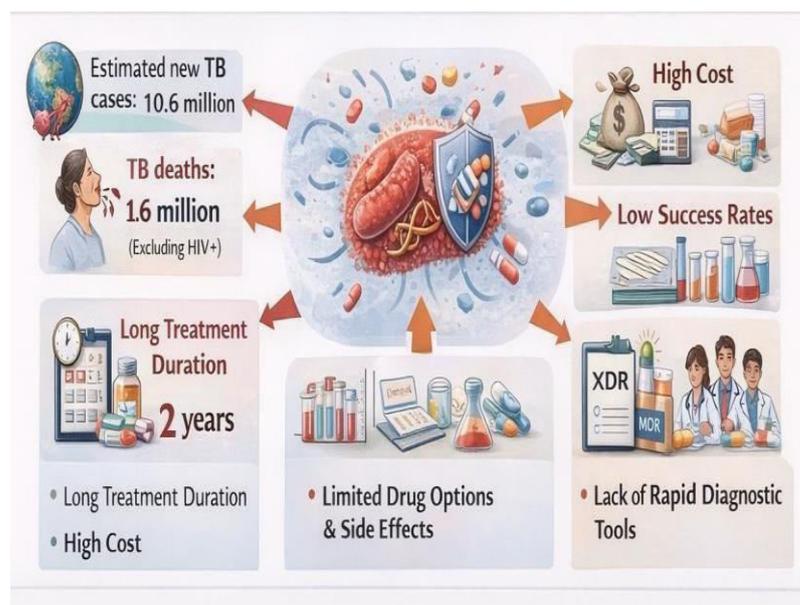


Fig.5 Challenges in treating MDR-TB

- a. Delayed and Incorrect Diagnosis – Inaccessibility of fast and accurate diagnostic techniques causes delay in diagnosing MDR-TB<sup>16, 34</sup>. Delayed diagnosis leads to ongoing transmission of MDR TB and treatment with unsuitable drugs<sup>1, 8</sup>.
- b. Long and Complex Treatment Regimens – MDR-TB can be cured with an MDR-TB regimen that usually involves an extensive period of therapy that can take up to 18–24 months<sup>8, 34</sup>. The nature of the treatment challenges patient compliance<sup>8, 31</sup>.
- c. Adverse Drug Reactions – Secondly, drugs used to treat tuberculosis are known to cause serious side effects, which include deafness, kidney problems, and stomach ailments, and would make the patient stop treatment mid-way<sup>8, 34</sup>.
- d. Treatment Adherence Issues – Some other reasons that may contribute to poor TB adherence may include socio-economic factors, lack of education among patients, stigma, and side effects<sup>8, 31</sup>.
- e. Limited Availability of Effective Drugs– Even new and effective anti-TB medication is not readily accessible in low- and middle-income countries because of cost and infrastructural constraints within healthcare facilities<sup>9, 34</sup>.
- f. Weak Healthcare Systems – There is insufficient laboratory capacity, health care professionals, and drug supply chains to manage MDR/RR-TB cases effectively<sup>31, 34</sup>.
- g. Transmission in Communities & Healthcare Settings – Crowding, inadequate infection control practices, or inadequate patient isolation are factors that facilitate the spread of drug-resistant TB<sup>1, 31</sup>.
- h. Co-infection with HIV – TB-HIV co-infection makes diagnosing and managing these diseases even more challenging due to drug interactions, toxicity, and impaired immune responses<sup>31, 34</sup>.
- i. Poor Hospital and Clinic Systems – A well-designed and the poor appreciation of the importance of TB treatment has resulted in the misuse of antibiotics, stopping treatment too soon, and the development of resistance<sup>8, 31</sup>.
- j. Economic Burden – The cost of treatment of MDR-TB is expensive not only for the health system but also for the patient<sup>8, 31</sup>.
- k. Lack of Research and Developments – The slow development of new drugs and a lack of investment in research in TB are some factors hindering the fight against drug-resistant strains of this infectious disease<sup>9, 30</sup>.
- l. Policy And Program Implementation Gaps – Ineffective implementation of National TB Control Programs, irregular monitoring, and, consequently, ongoing appearance of new cases of MDR-TB are observed<sup>31, 34</sup>.

### XI. LIMITATIONS

- a. Limited Availability of High-Quality Data – A major limitation of studies on MDR-TB has been that most of the existing literature has been coming from high-prevalence countries and has also varied in research capacity<sup>1,34</sup>.
- b. Heterogeneity of Study Designs – The Variations in the research design, diagnostic standards, treatment modalities, and outcome variables also detract from the ease of comparisons among the research findings<sup>8,34</sup>.
- c. Limited Access to Recent Data – Not all areas have information available on drug resistance to be able to assess existing trends in drug resistance in these areas<sup>34</sup>.
- d. Limited Evidence on Long-term Outcomes – There is a lack of longitudinal follow-up information on patients who have received treatment for MDR TB, specifically regarding rates of relapse, quality of life, as well as complications arising post-treatment<sup>8,34</sup>.
- e. Variation in Diagnostic Capabilities – Inadequate access to swift molecular diagnostic technology translates to late or missed detection of drug resistance<sup>16,34</sup>. This impinges on the accuracy of reported results<sup>7,16</sup>.
- f. Publication Bias – Studies with positive treatment outcomes or new treatment strategies are more likely to be published, which can lead to an overestimation of treatment success and an underrepresentation of failures<sup>8,34</sup>.
- g. Lack of Information on Paediatric and At-Risk Groups – Children, migrants, and other vulnerable groups are also inadequately represented as participants in MDR-TB research<sup>31,34</sup>.
- h. Restricted Assessment of Newer Agents and Regimens – However, data on the efficacy and safety, especially in real-life conditions, is still very limited among the new anti-TB medicines<sup>9,30</sup>.
- i. Predisposing Factors – However, variables such as HIV co-infections, nutritional status, and socio- economic variables are not uniformly considered, and this impacts data interpretation<sup>10,31</sup>.

### XII. DISCUSSION

Antimicrobial resistance (AMR) has recently come to be recognized as one of the most serious threats to global public health, with tuberculosis (TB) being an important contributor to the same<sup>1,31</sup>. The occurrence of multi-drug resistant tuberculosis (MDR-TB), which implies the bacterium's resistance to at least both isoniazid and rifampicin, can thus be seen as an exemplar of the more general phenomenon of antimicrobial resistance arising as a consequence of the biological evolution of microbes as well as the failure of health care systems<sup>6,31</sup>. The present article aims to put into perspective that MDR-TB, as an event, has biological as well as socio-economic aspects<sup>1,10</sup>. One of the most important contributing factors to MDR-TB is improper or incomplete anti-tubercular therapy<sup>6,8</sup>. Lack of patient compliance with long-term therapies due to adverse effects from medication and a failure to educate patients are major contributors to selecting resistant strains of *M. tuberculosis*<sup>8,31</sup>. Moreover, improper prescriptions in forms of inappropriate drug associations and undertreatment are also causing faster generations of TB resistance<sup>6,8</sup>. Such conditions are particularly observed in developing nations where high rates of TB are already present and healthcare facilities are less advanced<sup>1,31</sup>.

At the molecular level, resistance in *M. tuberculosis* arises primarily through chromosomal mutations rather than horizontal gene transfer, a feature so common in other bacterial pathogens<sup>4,6</sup>. The mutations involve genes such as *katG*, *inhA*, *rpoB*, *embB*, and *gyrA* that all confer a clinically significant reduction in the binding of the drug to its target or an alteration in drug activation<sup>4,5,11</sup>. The development of such mutations, especially because of extended exposure to ineffective concentrations of drugs, emphasizes the importance of early diagnosis and appropriate treatment regimens<sup>8,16</sup>. The emergence of XDR-TB and pre-XDR-TB adds further complexity to TB management and underscores the shortcomings of conventional antimicrobial therapy<sup>2,34</sup>. Resistance forms require longer treatment, the use of second-line or new drugs, and increase toxicity, costs, and poor outcomes<sup>8,34</sup>. While there are recent advances with bedaquiline, delamanid, and pretomanid, access remains variable and there are concerns about the potential development of resistance to newer agents<sup>9,30</sup>.

From a public health viewpoint, an MDR-TB situation indicates a problem with TB control programs and underlines the need to work on improving healthcare systems<sup>1,31</sup>. While the use of rapid test kits such as GeneXpert MTB/RIF and the line probe assay has increased the effectiveness of the initial detection of drug-resistant TB, access to these tools has not been regular<sup>7,16</sup>. The application of principles of antimicrobial stewardship in TB care would be vital to ensure rational use of medications, reduce the risk of developing drug-resistant TB, and conserve the effectiveness of new antitubercular drugs<sup>8,30</sup>. Moreover, social determinants such as poverty, malnutrition, and overlapping infection of HIV have been observed to play an important part in the transmission and management of MDR-TB<sup>10,31</sup>. In order to address these aspects effectively, patient-centred care and social protection programs become essential to enhance

compliance<sup>8,31</sup>. The involvement of healthcare professionals, including pharmacists, in counselling and monitoring adverse reactions to drugs is important to encourage compliance<sup>8,31</sup>.

### XIII. CONCLUSION

One of the most pressing and complex issues in global TB control is the ongoing emergence of MDR-TB<sup>1,34</sup>. The core reason for the rise in the emergence of MDR and other TB-resistant strains is poor healthcare infrastructure, development of drug resistance due to improper treatment practices, and community transmission of these strains<sup>6,8</sup>. Molecular techniques for DST have brought about a major revolution in the diagnosis of MDR-TB, and yet they are not easily accessible in resource-challenged settings<sup>7,16</sup>. Although patients yielding MDR and XDR TB pose a serious challenge to treatment targets, they can still be successfully cured after early diagnosis and treatment-initiation strategies based on suitable treatment regimens<sup>8,34</sup>. Home treatment strategies will certainly help patients in getting appropriate treatment and overcoming socio-economic barriers to adhere to treatment regimens<sup>8,15</sup>.

Antimicrobial resistance in tuberculosis, especially in its MDR form, is one of the biggest threats to global public health and tuberculosis control efforts<sup>1,31</sup>. The emergence of resistance to antituberculosis drugs like isoniazid and rifampicin is mainly due to improper use of drugs, lack of patient compliance, drug shortages, and lack of treatment monitoring<sup>6,8</sup>. These factors provide conditions for the survival and multiplication of *M. tuberculosis*, thereby causing higher transmission rates and morbidity and mortality rates<sup>1,31</sup>. For the management of an MDR-TB patient, second-line and newer medications would be needed, which tend to be more toxic, costly, and require longer treatment periods<sup>8,34</sup>. This would hamper the healthcare system considerably, especially in resource-limited countries<sup>31,34</sup>. Early proper diagnosis accomplished by modern methods of diagnosis like molecular techniques, prudent utilization of antimicrobial agents, strict compliance with internationally recommended regimens for management, and proper patient education are needed for the prevention of the emergence of resistant strains of the bacteria<sup>7,8,16</sup>.

Therefore, controlling multi-drug resistant TB requires a multi-faceted approach on the part of health professionals, policy makers, and TB patients themselves<sup>8,31</sup>. Improving national TB control programs, preserving good antimicrobial use practices, ensuring access to quality diagnosis and TB medications, and educating TB patients are essential for controlling MDR-TB and achieving the objective of sustained TB elimination<sup>1,8,31</sup>.

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