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Tuberculosis Epidemiology, Pathogenesis, Drugs and Drug Resistance Development: A Review

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Abstract

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis* and classified as pulmonary and extrapulmonary based on their site of infection. Anti-tuberculosis drugs developed since the 1940s and as their discovery resistance also developed against them. World health organization recognized tuberculosis as emergency public health in 1993.

Acquired and primary drug resistances are the common pathways for the development of anti-tuberculosis drug resistance. Acquired drug resistance is the result of inappropriate treatment, poor quality of the drugs and inadequate drug intake and primary drug resistance is due to exposure to the drug-resistant anti-tuberculosis. Types of anti-tuberculosis drug-resistant are multidrug-resistant tuberculosis is the result of resistance to isoniazid and rifampicin, extensively drug-resistant tuberculosis a consequence of resistance to isoniazid, rifampicin, fluoroquinolones and one of the second-line injectable drugs and totally drug-resistant tuberculosis is a resistance to all first and second-line anti-tuberculosis drugs.

Anti-tuberculosis drugs primarily actions are on protein synthesis, mycolic acid synthesis, DNA synthesis, folic acid synthesis, and ATP synthase. These drugs could produce bacteriostatic or bactericidal effects on the mycobacteria. The main resistance mechanism to the anti-tuberculosis drug is the mutation of the target gene accountable for the action of anti-tuberculosis drugs. This resistance to the anti-tuberculosis drug produces a devastating effect on public health. Therefore, further study should be conducted in the areas of finding a new target for the development of new anti-tuberculosis drugs.

Keywords: Tuberculosis; Epidemiology; Drug resistance

Abbreviations: ATP: Adenosine Tri Phosphate; BCG: Bacillus Calmette-Guerin; HIV: Human Immunodeficiency Virus; MDR TB: Multi Drug-Resistant Tuberculosis; MoHFDRE: Ministry of Health Federal Democratic Republic of Ethiopia; MTB: *Mycobacterium tuberculosis*; RIF: Rifampicin; TB: Tuberculosis; WGS: Whole Genome Sequencing; WHO: World Health Organization

Introduction

Tuberculosis is a chronic infectious and zoonotic disease caused by the *Mycobacterium tuberculosis* complex. It is accountable for a lung infection (pulmonary tuberculosis) and other body parts (extrapulmonary tuberculosis). Anti-tuberculosis drugs emerged since the 1940s and dramatically reduce mortality rates. In spite of highly efficacious treatment tuberculosis stay as a most public health constraint. Tuberculosis is ranked as the second cause of the mortality next to HIV infection. Tuberculosis declared as a global public health emergency since 1993 at a time of estimated 7-8 million cases and 1.3-1.6 million deaths occurred annually. In 2010 there were 8.8 million new cases of tuberculosis and 1.1 million deaths from tuberculosis among HIV negative and 0.35 million deaths from that HIV-associated tuberculosis and it is exacerbated due to the development of anti-tuberculosis drug resistance [1].

The emergence of resistance against anti-tuberculosis drug is the obstacle for the effectiveness of the treatment. Moreover, resistance to anti-tuberculosis drugs is a natural phenomenon occurring against *Mycobacterium tuberculosis* by the spontaneous chromosomal mutations. Inadequate tuberculosis treatment is accountable for the occurrence of drug-resistant *Mycobacterium tuberculo*sis. Even single chromosomal mutations direct the resistance to two or more anti-tuberculosis drugs [2].

World health organization report of 2009 ranked Ethiopia seventh in the world and third in Africa for the burden of tuberculosis in 2008. In Ethiopia estimated incidence of 378 new cases per 100,000 persons, 163 new smear-positive cases per 100,000 persons and prevalence of 579 per 100,000 populations [3]. Ethiopia registered 146,172 cases of tuberculosis in the year of 2009/10. Among these new cases of 139,261; new smear-positive 46,132 (33.1%); new smear-negative 49,037 (35.2%) and extrapulmonary tuberculosis 44,092 (31.6%) [4]. This

confirms that Ethiopia is endemic for the tuberculosis disease. According to drug resistance survey carried out in Ethiopia from 2003 to 2006 indicated that multidrug resistance tuberculosis is 11.8% in previously treated cases and 1.6% of newly diagnosed tuberculosis cases; include 5,200 cases annually [5].

Therefore, the objective of this paper is to review the status of anti-tuberculosis drug resistance.

Etiology and Routes of Transmission

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* complex. This complex includes *M. tuberculosis* (including subspecies *M. canetti*), *M. bovis*, *M. bovis* BCG, *M. africanum*, *M. caprae*, *M. microti* and *M. pinnipedii* [6]. Cough of a tuberculosis patient is a source of *Mycobacterium tuberculosis* and it disseminate to air during coughing. The persons who have inhaled air droplet and contact with TB patient become infected [7].

Epidemiology and Associated Factors of Tuberculosis

Tuberculosis is determined by the presence of poverty, malnutrition, overcrowding and incomplete health care system which are the predisposing factors [8]. In the latest time patients developing active tuberculosis is an estimated 9.6 million persons and 1.5 million deaths annually [8,9]. For instance, across the different countries the incidence of tuberculosis changes; in Western Europe 5 per 100,000 persons, whereas, 800 per 100,000 in South Africa [10]. According to the WHO, 5% of all new tuberculosis cases are due to multidrug-resistant tuberculosis. Moreover, MDR TB prevalence varies from region to regions. For example, MDR TB in eastern Europe and central Asia reaches up to 48% [9,11].

The two common pathways that lead to drug-resistant tuberculosis are acquired and primary drug resistance. Acquired drug resistance is resulted from inappropriate treatment, in the adequate or poor quality of drugs and inadequate drug intake in the presence of drug-susceptible tuberculosis. In the case of primary drug resistance direct exposure to the drug-resistant anti-tuberculosis. However, tuberculosis transmission or progression is prevented by various factors such as infection control and environmental interventions, good host immunity, latent tuberculosis treatment and high-quality diagnosis, treatment, patient support and management of drug-resistant tuberculosis [2,12]. While the increased transmission rate of drug-resistant tuberculosis aggravates the magnitude of tuberculosis burden [13].

Multidrug-resistant tuberculosis is resistant to isoniazid and rifampicin, but with or without resistance to other first-line drugs [14]. Extensive drug-resistant tuberculosis is resistant to isoniazid, rifampicin, and fluoroquinolones and any one of three-second line injectables (kanamycin, amikacin, and capreomycin). It is reported in 2006 as a severe form of tuberculosis [14,15]. Totally drug-resistant tuberculosis is a resistance to all first and second-line anti-tuberculosis drugs and it is reported after one year of extensive drug-resistant described. However, total drug-resistant tuberculosis definition still it is not recognized by the World Health Organization [14].

Extensively drug-resistant and totally drug-resistant tuberculosis developed as a consequence of failure to identify an appropriate treatment of multidrug-resistant tuberculosis patients [15,16]. The first case of totally drug-resistant tuberculosis reported in the USA from the patient who went to the USA to study English [17]. After that, it is reported in different places including Italy, Iran, India, and South Africa [18-21] Among the total cases of multidrug-resistant tuberculosis strains 10% are total drug-resistant tuberculosis [14].

Pathogenesis

Infection due to *Mycobacterium tuberculosis* could be an active or latent infection. Active infection is characterized by a wide range of granulomatous structures that includes bacterial laden, necrotic (caseating) lesions and central liquefaction, whereas latent infection is characterized by fibrotic and calcified lesions [22]. Mechanism of granulomatous lesions development is by the small and aerosolized particles of *Mycobacterium tuberculosis* reaches alveoli via inhalation then transported to tissue with the help of macrophages form aggregation with immune cells [23]. Disease development in immunocompromised and immunocompetent persons is different as consequences of immunocompromised persons develop poorly organized and noncaseating lesions, whilst immunocompetent persons produce a highly organized, caseating and cavitary lesions [24].

Drugs Used for Treatment of Tuberculosis and their Mechanism of Actions

Drugs used for the treatment tuberculosis classified as first and second line and new TB drugs based on their potency and safety issues.

First-line drugs

Isoniazid: Isoniazid commenced as an anti-tuberculosis drug since 1952 and act as a bactericidal and bacteriostatic for rapidly and slowly growing bacilli, respectively. It is also named as isonicotinic hydrazide and diffuses across *Mycobacterium tuberculosis* cell membrane [25]. The targets of isoniazid are KatG and inhA gene. KatG gene encodes two enzymes called catalase/peroxidase enzyme that activates prodrug and peroxynitrite involved in pathways of reactive nitrogen and oxygen intermediates [26,27]. InhA gene encodes NADH-dependent enoyl-Acyl Carrier Protein (ACP)-reductase that inhibits mycolic acid synthesis [28,29].

Rifampicin: Rifampicin was isolated from *Streptomyces mediterranei* in 1957 from soil sample at Lepetit Research Laboratories of France and used as an anti-tuberculosis agent since 1972 [30]. It is still utilized as the best choice of anti-tuberculosis drug. Rifampicin is lipophilic and diffuses across the cell membrane of *Mycobacterium tuberculosis*. The primarily targeted rpoB of DNA dependent-RNA polymerase β subunit and

rpoB uses four ribonucleotide triphosphates as substrates to catalyze transcription of DNA into mRNA. Rifampicin binds to the β subunit of DNA dependent-RNA polymerase and inhibits transcription of mycobacteria [31-34].

Ethambutol: Ethambutol is active against growing bacilli because of its bacteriostatic nature and commenced as an anti-tuberculosis drug since 1966. It hampers polymerization of cell wall component arabinogalactan and lipoarabinomannan and results in a buildup of intermediate arabinan biosynthesis D-arabinofuranosyl-P-decaprenol and bacteriostatic effect [35,36]. Arabinosyl transferase enzyme is a target for the action of ethambutol in both *Mycobacterium tuberculosis* and *Mycobacterium avium*. The enzyme is encoded by the embCAB gene organized as an operon and engaged in the arabinogalactan synthesis [37,38].

Pyrazinamide: Pyrazinamide activity against *Mycobacterium tuberculosis* depends on the acidity and anaerobic conditions [32]. It is activated to pyrazines acid by enzyme pyrazinamide/nicotinamidase that encoded by gene pncA [39]. Acidic condition favors the formation of protonated pyrazinoic acid that passes via a membrane and accumulated in the cell membrane of *Mycobacterium tuberculosis* which interrupts cell membrane potential and alters membrane transport [40]. RpsA gene encodes 30S ribosomal protein S1 responsible for the mRNA translation [41]. Gene panD participates in pantothenate biosynthesis by converting L-aspartate into beta-alanine [42]. Pyrazinamide new target, clpC1 (Rv3596c) that encode an ATP dependent ATPase is responsible for protein degradation by complex formation with protease clpP1 and clpP2 [43].

Streptomycin: Streptomycin isolated from the soil microorganism *Streptomyces griseus* in 1943 and the first antibiotic cure for tuberculosis [44,45]. It is active against growing bacilli, but not against non-growing or intracellular bacilli [46]. It targets both rpsl and rrs genes that encode 30S ribosomal protein S12 and 16S rRNA, respectively and finally inhibit the instigation of the translation in the protein synthesis [47,48].

Second-line drugs

Para-amino salicylic acid: There are two mechanisms of action for para-amino salicylic acid to produce the desired action. Firstly, inhibit folic acid synthesis by the action of dihydropteroate synthase and dihydrofolate synthase that generates hydroxyl dihydrofolate antimetabolite which inhibits dihydrofolate reductase enzyme responsible for the synthesis of folic acid [49]. Secondly, inhibit cell wall component mycobactin synthesis by reducing uptake of iron [32].

Ethionamide: Two genes play a role in the mechanism of actions ethionamide are ethA and inhA. EthA regulated by the transcriptional repressor ethR [50]. The mechanism of action of the ethionamide is a disruption of mycolic acid synthesis by which monooxygenase enzyme activated ethionamide that binds to NAD^+ and forms an adduct which inhibits enoyl acyl-ACP reductase enzyme [51-54].

Cycloserine: Cycloserine is a product of the cyclic derivative of serine hydroxamic acid and terizidone and isolated from *Streptomyces orchidaceous* in the 1950s. Cycloserine mechanism of action is by interfering with mycobacterial cell wall synthesis through inhibition of L-alanine racemase enzyme encoded by alrA that produce D-alanine from L-alanine and D-phenylalanine synthetase enzyme indispensable for the formation of peptidoglycan and cell wall synthesis by incorporation of D-alanine into pentapeptide [55-57].

Fluoroquinolones: Fluoroquinolones discovered as a derivative of chloroquine antimalarial drug in the 1960s and used in human and veterinary medicine as a bactericidal agent [58]. Mechanism of action of the fluoroquinolones is primarily depended on the blocking of mycobacterial DNA replication by binding to α and β subunits of DNA gyrase (gyrA and gyrB), which catalyze the supercoiling of DNA and finally, inhibits DNA synthesis [59,60].

Aminoglycosides and polypeptides: This group includes aminoglycosides (kanamycin, amikacin) and polypeptides (capreomycin, viomycin). The common features of these antibiotics are their mechanism of action inhibiting protein synthesis. Kanamycin and amikacin alter 16S rRNA and capreomycin and viomycin interfere with small and large subunits of the 70S ribosome [61-63].

Linezolid: Linezolid is a group of oxazolidinone that interrupt an early step in protein synthesis through binding to the assembly of the 23S ribosomal RNA of the 50S subunit. The gene rplC and rrl are involved in the mechanical action of Linezolid. The rplC gene possesses 654 bp in length that encodes 50S ribosomal L3 protein to contribute to the synthesis of the ribosomal peptidyltransferase. Hence, rrl gene possesses 3138 bp length that encodes 23S ribosomal RNA [64].

Newer TB drugs

Newer tuberculosis drugs emerged against MDR TB because of the discovery of the novel targets in the *Mycobacterium tuberculosis*.

Bedaquiline or TMC207: Bedaquiline is a member of diarylquinolines and bactericidal. ATP demanded by mycobacteria is generated by the atpE gene by encoding subunit C of the ATP synthase. Mechanism of action of the bedaquiniline involves blocking the proton pump of ATP synthase of *Mycobacterium tuberculosis* then depletes energy demand of both non replicating (dormant) and replicating mycobacteria and at the end result in cell death [65,66].

Delamanid or OPC 67683: Mycobacterial F420 coenzyme system component deazaflavin dependent nitroreductase and F420-dependent glucose 6-phosphate dehydrogenase enzyme are encoded by F420 coenzyme genes ddn and fgd1 gene, respectively [25,57]. Delamanid is a derivative of dihydronitroimidazooxazole and activated by deazaflavin dependent nitroreductase enzyme (Rv3547). Delamanid acts through interrupting the synthesis of the mycobacterial cell wall component. By means of radical intermediate produced during activation of delamanid between desnitroimidazooxazole derivative and delamanid inhibit the synthesis of methoxy-and keto-mycolic acid which is a crucial component of the

mycobacterial cell wall. It is active against growing and non-growing mycobacteria [67,68].

PA-824: PA-824 is a derivative of nitroimidazole and activated by deazaflavin dependent nitroreductase enzyme as that of delamanid. Mechanism action of PA-824 is not clear but could be described as its' activity in replicating and non-replicating mycobacteria. In aerobically replicating mycobacterial cell PA-824 disrupts mycolic acid synthesis by the accumulation of hydroxymycolates instead of ketomycolates [67,69,70]. Accordingly, in hypoxic non replicating mycobacteria, PA-824 release Nitric oxide (NO) that interfere with cytochrome oxidase to disrupt energy metabolism of the cell wall [71,72].

SQ-109: SQ-109 is a synthetic analogous of ethambutol. The mechanism of action of the SQ-109 is not clear and has no inhibition activity against secreted Ag85 mycolyltransferase enzyme. Rather SQ-109 causes accumulation of trehalose monomycolate a precursor of trehalose dimycolate by hindering assembles of mycolic acids into the bacterial cell wall core. Mmpl3 is a target of SQ-109 and transporter of trehalose monomycolate of the mycobacteria [73].

Mechanism of Resistance to the Anti-Tuberculosis Drug

Different mechanisms of resistance to anti-tuberculosis drugs emerged because of the mycobacteria undergo several mutations to overcome harsh environmental conditions. Mutated genes are those responsible for the activation of anti-TB drugs and synthesis components of *Mycobacteria* cell structure.

First-line drugs

Isoniazid: Resistance to the isoniazid associated with the mutation of KatG and inhA gene. KatG gene mutant S315T cause multidrug resistance by reducing the ability of KatG gene that converts isoniazid to isonicotinic acid which is a precursor for the formation of INH-NAD adducts [74-76]. In addition, a new KatG gene mutant L101R changes hydrophobic leucine to hydrophilic arginine and result in conformational alteration of protein binding site and hinders bioactivation [77].

Mutations in different positions of inhA gene regulatory region includes -15C/T, -8T/C, -15/T and -17C/T related with resistance [57,77-79]. Recent studies reported that mutation of inhA regulatory region together with mutation of inhA coding region end up in high resistance to isoniazid and cross-resistance to ethionamide that structurally related to isoniazid [80]. In both resistant and susceptible strain to isoniazid, mutations reported were Rv0340-0343, fadE24, efpA and KasA that demand further studies on their resistance mechanism [81].

Rifampicin: Site responsible for the rifampicin resistance is a "hot spot region" of 81bp of rpoB called RIF-resistance determining the region (RRDR) that covers 507-533 codons and principally mutation in codons of 516, 526 and 531 [82,83]. Cross-resistance to rifabutin occurred at 532 codon mutation in the rpoB gene that changes serine to leucine [77,83,84]. Compulsatory mutation discovered in rpoA and rpoC which encodes α and β' subunits of RNA polymerase, respectively [85]. The importance of these compulsatory mutations is for reinstating fitness and the emergence of multidrug-resistant strains [86].

Ethambutol: Ethambutol resistance is originated from a mutation of an embCAB operon that causes changes in the site of drug-protein binding [87]. Potential ethambutol resistance marker is the mutation of embB 306, but about 30% resistance is not related to embB gene mutation [88-90] About 70% of mutation in codons of 306, 406 or 497, 13% of mutation between codons 296 and 426, 15% mutations in the embed-embA intergenic region and mutation of ubiA gene that encode for a decaprenylphosphoryl-5-phosphoribose (DPPR) synthase along with mutation in embB correlated with high resistance to ethambutol [91,92]. The Minimum Inhibitory Concentration (MIC) of ethambutol increases due to mutations in genes of embB, embC and genes involved in the biosynthesis and utilization pathway of the decaprenylphosphoryl-beta-D-arabinose (DPA) called Rv3806C and Rv3792 [93,94].

Pyrazinamide: Pyrazinamide resistance is associated with mutations of pncA, rpsA, panD and clpP1 [95,96]. Hence, mutations of pncA gene is majorly responsible for the resistance that occurs especially at nucleotides of 359 and 374 and 82-262 bp regulatory regions, but no mutations detected at 561bp pncA gene [97,98]. Deletion of alanine at 438bp and overexpression of rpsA gene increases resistance to the Pyrazinamide [41].

Streptomycin: The primary cause of streptomycin resistance are mutations of rpsl, gidB and rrs [99,100] Mutation in rpsl is because of the replacement of lysine by arginine at positions 43 and 88 and in gidB conferring mutation to A80P gene product by targeting methylguanosine methyltransferase [100]. In rrs mostly mutations in the nucleotides 530 and 915 develop resistance and resistance to streptomycin is occurred commonly because of mutations in rpsl and rrs gene [101].

Second-line drugs

Para-amino salicylic acid: A mutation of Thr202Ala in thyA gene is related with resistance to para amino salicylic acid. In addition, mutation to folC gene is responsible for resistance.

Ethionamide: Mutations in the ethA or ethR and inhA or its promoter result in resistance to ethionamide and isoniazid [50]. High resistance against ethionamide and isoniazid is due to mutations in the inhA gene of -15C to -15T in the promoter region, S94A (Serine to alanine) and I94T (Isoleucine to threonine) [80].

Cycloserine: Cycloserine target in *Mycobacterium tuberculosis* is not well studied. However, alrA overexpression results in resistance [102].

Fluoroquinolones: Mutations of the gyrA and gyrB are responsible for the resistance to the fluoroquinolones. Resistance determining regions of gyrA and gyrB are 74-113 and 500-540 codons, respectively [103,104]. Mutations at different positions of gyrA Ala-74, Gly-88, Ala-90, Ser-91 and Asp-94 end in resistance [105]. Hence, Mutation to gyrB in clinical isolates is less common and being low resistant to fluoroquinolones [106].

But, synchronization of mutations of gyrA and gyrB, Ala543Val (gyrB)-Asp94Asn/Asp94Gly (gyrA) and Asn538Ile (gyrB)-Asp94Ala (gyrA) leads to high resistance [107].

Aminoglycosides and polypeptides: It consists aminoglycosides (kanamycin and amikacin) and polypeptides (capreomycin and viomyocin). Mutation to rrs gene at the position of 1,400, 1401 and 1,483 bp associated with high level resistance to both kanamycin and amikacin [108,109]. Hence, the mutation of rrs gene at the codon A1401G is related to high-level resistance to the kanamycin and amikacin as well as cross-resistance to capreomycin. In addition, resistance to the capreomycin associated with mutation of C1402T or G1484T and result in cross-resistance to kanamycin and viomycin [110,111].

Linezolid: Resistance to the linezolid is due to the mutation of the target genes. The mutation T460C in rplC gene plays a great role in the resistance to the linezolid and mutations of G2576T and G2061T in rrl gene increases minimum inhibitory concentrations. However, mutations of these genes account only 29.4% of linezolid resistance to the *Mycobacterium tuberculosis* [112]. As a result, further study required to explore the resistance mechanisms of linezolid.

Newer TB drugs

Bedaquiline: Mutations of A63P and I66M of atpE gene associated with resistance to bedaquiline; mutations in Rv0678 and pepQ are observed in wild type population and it controls the significant mechanism of clinical resistance [113].

Delamanid: Mutations in ddn and fgd1 result in resistance to the Delamanid [114].

PA-824: The main way of resistance to the PA-824 are the nitroimidazole-oxazine specific protein that causes structural changes to the drug and mutations of fdg1 [70,114].

SQ-109: Mmpl3 gene mutation leads to the development of resistance to the SQ-109 [115]. Hence, the up-regulation of ahpc gene plays a role in the development of resistance against isoniazid, ethambutol, and SQ-109 [116].

Management of Anti-Tuberculosis Drug Resistance

Management of the multidrug-resistant tuberculosis is very complex because of drugs used are toxic and administered for a long period of time than susceptible tuberculosis accompanied with a lower likelihood of treatment success [117]. Therefore, the following things should be followed:

- Isoniazid and rifampicin drugs rapid susceptibility test: This assumption is to reduce the delay to start the correct second-line therapy and for the purpose to increase cure, decrease mortality, reduce additional drug resistance development and reduce the possibility of failure and relapse [118]. Gene Xpert MTB/ RIF is sufficient to start a second line tuberculosis regimen by the patient, but confirmation by the line probe assay is required due to the probability of the false-positive results
- Combinations of sputum smear microscopy and culture: This assumption is to indicate that only the smear microscope could lead to delayed detection of failure. Simultaneous use of sputum smear microscopy and culture test leads to differentiate patients bacteriologically positive or relapse back to positive after initially converted to negative [119]
- Drugs included in the treatment regimen of multidrug-resistant tuberculosis are fluoroquinolones, later generation fluoroquinolones (levofloxacin, moxifloxacin) and ethionamide. In the treatment of multidrug-resistant tuberculosis four-second line anti-tuberculosis drugs expected to be effective and for the intensive phase pyrazinamide should be included. Treatment regimens of multidrug-resistant tuberculosis include at least pyrazinamide, fluoroquinolones, injectable or parenteral agent, ethionamide and either cycloserine or para-aminosalicylic acid should be included [119]
- In the treatment of the multi-drug resistant tuberculosis, an intensive phase requires at least 8 months duration and total treatment duration required at least 20 months for no previous multidrug-resistant tuberculosis treatment. The main purposes were to prevent death, the transmission of multidrug-resistant tuberculosis, avoid harms and minimize the use of resources. Following initiation of anti-tuberculosis treatment with in the first 8 weeks regardless/irrespective of CD4 cell count, antiretroviral therapy is given to all patients with the HIV and drug-resistant tuberculosis that demand second-line anti-tuberculosis drugs [119,120]
- In the extensively drug-resistant tuberculosis, the rate of cure is lower than multi drug-resistant tuberculosis. Otherwise, the principles of management are similar to the multi-drug resistant tuberculosis. The optimum number of drugs and duration of treatment are still uncertain. However, at least six groups for the intensive phase and four in the continuation phase with the highest treatment success. In addition, 6-9 months duration for the intensive phase and 20-25 months for the total duration of treatment required [119,120]
- New drugs such as bedaquiline and delamanid and new combination regimen enhance cure rate of extensively drug-resistant tuberculosis. In addition, later generation of fluoroquinolones (moxifloxacin) also significantly improved treatment outcomes [121-127]

Conclusion and Future Prospects

Tuberculosis is a major disease that constrains public health. It is caused by *Mycobacterium tuberculosis* and effective anti-tuberculosis drugs developed against TB. These drugs are classified as first and second line and new drugs based on their discovery time and effectiveness. However, drug resistance emerged because of bacteria undergoes revolution to escape harsh environment by chromosomal mutations.

Actively developing resistance and factors that propagate resistance development in the patient are still poorly understood and demands further explanation. Retrieval of mutation resistance in mycobacteria developed dynamically under antibiotic pressure for a long time. The relationship

between drug resistance, fitness, and virulence of the organism requires further study.

The current rapid diagnostic gene Xpert MTB/RIF and line probe assays are limited in their ability to produce a comprehensive resistance profile. For this reason, rapid WGS is the most promising utility for the drug-resistant tuberculosis diagnosis. The main strategy to diminish drug resistance crisis is a personalized treatment that suggests the potential to improve treatment outcomes. It is by a means of limiting therapeutic regimen to efficacious drugs and then reduction of unnecessary pill burden and significantly reducing side effects of the current treatment.

References

1. https://apps.who.int/iris/bitstream/handle/10665/44593/9789241501569_eng.pdf
2. Ministry of Health, Federal Democratic Republic Of Ethiopia (MoHFDRE) (2013) Guidelines on Programmatic Management of Drug-Resistant Tuberculosis in Ethiopia. 2nd Ed. Addis Ababa, Ethiopia.
3. World Health Organization (WHO) (2009) Global Tuberculosis control epidemiology, strategy, financing. Geneva, Switzerland.
4. Ethiopian Health and Nutrition Research Institute (EHNRI) (2011) First Ethiopian National Population-based Tuberculosis Prevalence Survey. Addis Ababa, Ethiopia.
5. World Health Organization (WHO) (2008) Antituberculosis resistance in the world. Report No. 4. Geneva, Switzerland.
6. Health and Social Services (2014) Basic facts about Tuberculosis: TB Control: -Yukon Communicable Disease Control
7. Kampala T, Shenoi VS, Friedland G (2013) Transmission of Tuberculosis in resource-limited settings. Curr HIV/AIDS Rep 10: 3.
8. Sulis G, Roggi A, Matteeli A, Raviglione MC (2014) Tuberculosis: epidemiology and control. Mediterr J Hematol Infect Dis 6: e2014070.
9. World Health Organization (WHO) (2015) Global tuberculosis report. Geneva, Switzerland.
10. Vynnycky E, Sumner T, Fielding KL, Lewis JJ, Cox AP, et al. (2015) Tuberculosis control in South African gold mines: mathematical modeling of a trial of community-wide isoniazid preventive therapy. Am J Epidemiol 181: 619-632.
11. Acosta CD, Dadu A, Ramsay A, Dara M (2014) Drug-resistant tuberculosis in Eastern Europe: challenges and ways forward. Public Health Action 4: S3-12.
12. https://www.intechopen.com/books/tuberculosis-current-issues-in-diagnosis-and-management/epidemiology-of-multidrug-resistant-tuberculosis-mdr-tb-
13. Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, et al. (2006) Global incidence of multidrug-resistant tuberculosis. J Infect Dis 194: 479-485.
14. World Health Organization (WHO) (2012) Totally drug-resistant tuberculosis: a WHO consultation on the diagnostic definition and treatment options. Geneva, Switzerland.
15. Centers for Disease Control and Prevention (CDC) (2006) Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs-worldwide, 2000-2004. MMWR Morb Mortal Wkly Rep 55: 301-305.
16. Masjedi MR, Farnia P, Sorooch S, Pooramiri MV, Mansoori SD, et al. (2006) Extensively drug-resistant tuberculosis: 2 years of surveillance in Iran. Clin Infect Dis 43: 841-847.
17. http://www.nbcnews.com/id/34516639/ns/health-infectious_diseases/t/danger-home-rare-form-tb-comes-us/#.XSwfCegzbIU
18. Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM (2007) First tuberculosis cases in Italy resistant to all tested drugs. Euro Surveill 12: e070517.
19. Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C (2012) Totally drug-resistant tuberculosis in India. Clin Infect Dis 54: 579-581.
20. Klopper M, Warren RM, Hayes C, Van Pittius NC, Streicher EM, et al. (2013) Emergence and spread of extensively and totally drug-resistant tuberculosis, South Africa. Emerg Infect Dis 19: 449-455.
21. Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, et al. (2009) Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest 136: 420-425.
22. Kaplan G, Post FA, Moreira AL, Wainwright H, Kreiswirth BN, et al. (2003) Mycobacterium tuberculosis growth at the cavity surface: A microenvironment with failed immunity. Infect Immun 71: 7099-7108.
23. Connolly EL, Edelstein HP, Ramakrishnan L (2007) Why is long term therapy required to cure Tuberculosis. Plos/Med 4: e120.
24. Hernandez-Pando R, Jeyanathan M, Mengistu G, Aguilar D, Orozco H, et al. (2000) Persistence of DNA from Mycobacterium tuberculosis in superficially normal lung tissue during latent infection. Lancet 356: 2133-2138.
25. Bardou F, Raynaud C, Ramos C, Laneelle MA, Laneelle G (1998) Mechanism of isoniazid uptake in Mycobacterium tuberculosis. Microbiol 144: 2539-2544.
26. Zhang Y, Heym B, Allen B, Young D, Cole S (1992) The catalase-peroxidase gene and isoniazid resistance of Mycobacterium tuberculosis. Nature 358: 591-593.
27. Suarez J, Ranguelova K, Jarzecki AA (2009) An oxyferrous heme/protein-based radical intermediate is catalytically competent in the catalase reaction of Mycobacterium tuberculosis catalase-peroxidase (KatG). J Biol Chem 284: 7017-7029.
28. Rawat R, Whitty A, Tonge PJ (2003) The isoniazid-NAD adduct is a slow, tight-binding inhibitor of InhA, the Mycobacterium tuberculosis enoyl reductase: Adduct affinity and drug resistance. Proc Natl Acad Sci 100: 13881-13886.
29. Timmins GS, Master S, Rusnak F, Deretic V (2004) Nitric oxide generated from isoniazid activation by KatG: source of nitric oxide and activity against Mycobacterium tuberculosis. Antimicrob Agent Chemother 48: 3006-3009.
30. Palomino JC, Martin A (2014) Drug resistance mechanisms in Mycobacterium tuberculosis. Antibiotics 3: 317-340.
31. Blanchard JS (1996) Molecular mechanisms of drug resistance in Mycobacterium tuberculosis. Annu Rev Biochem 65: 215-239.
32. Wade MM, Zhang Y (2004) Mechanisms of drug resistance in Mycobacterium tuberculosis. Front Biosci 9: 975-994.
33. Carlos JC, Martin A (2013). Tuberculosis clinical trial update and the current anti tuberculosis drug portfolio. Curr Med Chem 20: 3785-3796.
34. Piccaro G, Pietraforte D, Giannoni F, Mustazzolu A, Fattorini L (2014) Rifampin induces hydroxyl radical formation in

Mycobacterium tuberculosis. Antimicrob Agents Chemother 58: 7527-7533.

35. Mikusova K, Huan H, Yagi T, Holsters M, Vereecke D, et al. (2005) Decaprenylphosphoryl arabinofuranose, the donor of the D-arabinofuranosyl residues of mycobacterial arabinan, is formed via a two-step epimerization of decaprenylphosphoryl ribose. J Bacteriol 187: 8020-8025.

36. Wang F, Jain P, Gulten G, Liu Z, Feng Y, et al. (2010) Mycobacterium tuberculosis dihydrofolate reductase is not a target relevant to the antitubercular activity of isoniazid. Antimicrob Agents Chemother 54: 3776-3782.

37. Zhang Y, Yew WW (2009) Mechanisms of drug resistance in Mycobacterium tuberculosis. Int J Tuberc Lung Dis 13: 1320-1330.

38. Mikusová K, Slayden RA, Besra GS, Brennan PJ (1995). Biogenesis of the mycobacterial cell wall and the site of action of ethambutol. Antimicrob Agents Chemother 39: 484-489.

39. Scorpio A, Zhang Y (1996) Mutations in pncA, a gene encoding pyrazinamidase/nicotinamidase, cause resistance to the antituberculous drug pyrazinamide in tubercle bacillus. Nat Med 2: 662-667.

40. Zhang Y, Wade MM, Scorpio A (2003) Mode of action of pyrazinamide: disruption of Mycobacterium tuberculosis membrane transport and energetics by pyrazinoic acid. J Antimicrob Chemother 52: 790-795.

41. Shi D, Li L, Zhao Y, Jia Q, Li H, Coulter C, et al. (2011b) Characteristics of embB mutations in multidrug-resistant Mycobacterium tuberculosis isolates in Henan, China. J Antimicrob Chemother 66: 2240-2247.

42. Shi W, Chen J, Feng J, Cui P, Zhang S, et al. (2014) Aspartate decarboxylase (PanD) as a new target of pyrazinamide in Mycobacterium tuberculosis. Emerg Microbes Infect 3: e58.

43. Zhang S, Chen J, Shi W, Cui P, Zhang J, et al. (2017) Mutation in clpC1 encoding an ATP-dependent ATPase involved in protein degradation is associated with pyrazinamide resistance in Mycobacterium tuberculosis. Emerg Microbes Infect 6: e8.

44. https://www.elsevier.com/books/biotechnology-for-beginners/renneberg/978-0-12-801224-6

45. https://books.google.co.in/books?hl=en&lr=&id=h4GuDQAAQBAJ&oi=fnd&pg=PT13&dq=45.%09Torok+E,+Moran+Ed.+and+Cooke+F+(2009)+Oxford+Handbook+of+Infectious+Diseases+and+Microbiology.+OUP+Oxford.&ots=Be2wiXUJ3g&sig=glt_Fqx4PIX_GmEbHZrl1UFIpOg#v=onepage&q&f=false

46. Heifets L, Desmond E (2005) Clinical Mycobacteriology Laboratory. In: Cole S, Eisenach K, McMurray D, Jacobs W Jr eds. Tuberculosis and the tubercle bacillus, Washington DC, USA: ASM Press: 9949-9970.

47. Sharma D, Lata M, Faheem M, Ullah Khan A, Joshi B, et al. (2015) Cloning, expression and correlation of Rv0148 to amikacin and kanamycin resistance. Curr Proteomics 12: 96-100.

48. Chakraborty S, Gruber T, Barry CE, Boshoff HI, Rhee KY (2013) Para-aminosalicylic acid acts as an alternative substrate of folate metabolism in Mycobacterium tuberculosis. Science 339: 88-91.

49. Zheng J, Rubin JE, Bifani P, Mathys V, Lim V, et al. (2013) Discovery of the Mechanism of action of a critical Tuberculosis drug: Para-Aminosalicyclic Acid is a prodrug targeting Dihydrofolate reductase in Mycobacterium tuberculosis. J Biol Chem 288: 23447-23456.

50. Carette X, Blondiaux N, Willery E, Hoos S, Lecat-Guillet N, et al. (2011). Structural activation of the transcriptional repressor EthR from Mycobacterium tuberculosis by single amino acid change mimicking natural and synthetic ligands. Nucleic Acids Res 40: 3018-3030.

51. Quemard A, Laneelle G, Lacave C (1992) Mycolic acid synthesis: a target for Ethionamide in mycobacteria? Antimicrob Agents Chemother 36: 1316-1321.

52. Vanneli AT, Dykman A, Ortiz de Montellano RP (2002) The antituberculosis drug ethionamide is activated by a flavoprotein monooxygenase. J Biol Chem 277: 12824-12829.

53. Grant SS, Wellington S, Kawate T, Desjardins CA, Silvis MR, et al. (2016) Baeyer-Villiger Monooxygenases EthA and MymA are required for activation of replicating and non-replicating Mycobacterium tuberculosis inhibitors. Cell Chem Biol 23: 666-677.

54. Mori G, Chiarelli LR, Riccardi G, Pasca MR (2017) New prodrugs against tuberculosis. Drug Discov Today 22: 519-525.

55. Zhang Y (2005) The magic bullets and Tuberculosis drug targets. Annu Rev Pharmacol Toxicol 45: 529-564.

56. Prosser AG, Carvalho SLP (2013) Reinterpreting the mechanism of inhibition of Mycobacterium tuberculosis D-alanine:D-alanine ligase by D-cycloserine. Biochem 52: 7145-7149.

57. Zhang Y, Yew W (2015) Mechanisms of drug resistance in Mycobacterium tuberculosis: update 2015. Int J Tuberc Lung Dis 19: 1276-1289.

58. Pallo-zimmerman LM, Byron J, Graves TK (2010) Fluoroquinolones: then and now. Compend Contin Educ Vet 32: 1-9.

59. Drlica K, Xu C, Wang JY, Burger MR, Malik M (1996). Fluoroquinolone action in Mycobacteria: Similarity with effects in Escherichia coli and detection by cell lysate viscosity. Antimicrobial Agents and Chemotherapy 40: 1594-1599.

60. Aubry A, Pan XS, Fisher LM, Jarlier V, Cambau E (2004) Mycobacterium tuberculosis DNA gyrase: interaction with quinolones and correlation with antimycobacterial drug activity. Antimicrob Agent Chemother 48: 1281-1288.

61. Alangaden GJ, Kreiswirth BN, Aouad A, Khetarpal M, Igno FR, et al. (1998) Mechanism of resistance to amikacin and kanamycin in Mycobacterium tuberculosis. Antimicrob Agents Chemother 42: 1295-1297.

62. Suzuki Y, Katsukawa C, Tamaru A, Abe C, Makino M, et al. (1998) Detection of kanamycin-resistant Mycobacterium tuberculosis by identifying mutations in the 16s rRNA gene. J Clin Microbiol 36: 1220-1225.

63. Stanley RE, Blaha G, Grodzicki RL, Strickler MD, Steitz TA (2010) The structures of the anti-tuberculosis antibiotics viomycin and capreomycin bound to the 70S ribosome. Nat Struct Mol Biol 17: 289-293.

64. Williams K, Stover C, Zhu T, Tasneen R, Tyagi S, et al. (2009) Promising antituberculosis activity of the oxazolidinone PNU-100480 relative to that of linezolid in a murine model. Antimicrob Agents Chemother 53: 1314-1319.

65. Andries K, Verhasselt P, Guillemont J, Göhlmann HW, Neefs JM, et al. (2005) A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 307: 223-227.

66. Koul A, Dendouga N, Vergauwen K, Molenberghs B, Vranckx L, et al. (2007) Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol 3: 323-324.

67. Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, et al. (2006) OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 3: e466.

68. Gurumurthy M, Tathagate M, Cynthia DS, Singh R, Niyomrattanakit P, et al. (2012) Substrate specificity of the deazaflavin dependent nitroreductase from Mycobacterium tuberculosis responsible for the bioreductive activation of bicyclic nitroimidazoles. FEBS J 279: 113-125.

69. Stover CK, Warrener P, van Devanter DR, Sherman DR, Arain TM (2000) A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature 405: 962-966.

70. Manjunatha UH, Boshoff H, Dowd CS, Zhang L, Albert TJ, et al. (2006) Identification of a nitroimidazo-oxazine-specific protein involved in PA-824 resistance in Mycobacterium tuberculosis. Proc Natl Acad Sci 103: 431-436.

71. Rao SP, Alonso S, Rand L, Dick T, Pethe K (2008) The proton motive force is required for maintaining ATP homeostasis and viability of hypoxic, non-replicating Mycobacterium tuberculosis. Proc Natl Acad Sci 105: 11945-11950.

72. Singh R, Manjunatha U, Boshoff HI, Ha YH, Niyomrattanakit P, et al. (2008) PA-824 kills nonreplicating Mycobacterium tuberculosis by intracellular NO release. Science 322: 1392-1395.

73. Tahlan K, Wilson R, Kastrinsky DB, Arora K, Nair V, et al. (2012) SQ109 targets MmpL3, a membrane transporter of trehalose monomycolate involved in mycolic acid donation to the cell wall core of Mycobacterium tuberculosis. Antimicrob Agents Chemother 56: 1797-1809.

74. Bantubani N, Kabera G, Connolly C, Rustomjee R, Reddy T, et al. (2014) High rates of potentially infectious tuberculosis and multidrug-resistant tuberculosis (MDR-TB) among hospital inpatients in Kwazulu Natal, South Africa indicate risk of nosocomial transmission. PLoS ONE. 9: e90868.

75. Seifert M, Catanzaro D, Catanzaro A, Rodwell TC (2015) Genetic mutations associated with isoniazid resistance in Mycobacterium tuberculosis: a systematic review. PLoS ONE 10: e0119628.

76. Aye KS, Nakajima C, Yamaguchi T, Win MM, Shwe MM, et al. (2016) Genotypic characterization of multidrug-resistant Mycobacterium tuberculosis isolates in Myanmar. J Infect Chemother 22: 174-179.

77. Datta G, Nieto LM, Davidson RM, Mehaffy C, Pederson C, et al. (2016) Longitudinal whole-genome analysis of pre and post drug treatment Mycobacterium tuberculosis isolates reveals progressive steps to drug resistance. Tuberculosis 98: 50-55.

78. Fenner L, Egger M, Bodmer T, Altpeter E, Zwahlen M, et al. (2012) Effect of mutation and genetic background on drug resistance in Mycobacterium tuberculosis. Antimicrob Agents Chemother 56: 3047-3053.

79. Muller B, Streicher E, Hoek K, Tait M, Trollip A, et al. (2011) inhA promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa? Int J Tuberc Lung Dis 5: 344-351.

80. Machado D, Perdigão J, Ramos J, Couto I, Portugal I, et al. (2013) High-level resistance to isoniazid and ethionamide in multidrug-resistant Mycobacterium tuberculosis of the Lisboa family is associated with inhA double mutations. J Antimicrob Chemother 68: 1728-1732.

81. Vilcheze C, Wang F, Arai M, Hazbón MH, Colangeli R, et al. (2006) Transfer of a point mutation in Mycobacterium tuberculosis inhA resolves the target of isoniazid. Nat Med 12: 1027-1029.

82. Ocheretina O, Escuyer VE, Mabou MM, Royal-Mardi G, Collins S, et al. (2014) Correlation between genotypic and phenotypic testing for resistance to rifampin in Mycobacterium tuberculosis clinical isolates in Haiti: investigation of cases with discrepant susceptibility results. PLoS ONE 9: e90569.

83. Thirumurugan R, Kathirvel M, Vallayyachari K, Surendar K, Samrot AV, et al. (2015) Molecular analysis of rpoB gene mutations in rifampicin resistant Mycobacterium tuberculosis isolates by multiple allele-specific polymerase chain reaction in Puducherry, South India. J Infect Public Health 8: 619-625.

84. Mboowa G, Namaganda C, Ssengooba W (2014) Rifampicin resistance mutations in the 81 bp RRDR of rpoB gene in Mycobacterium tuberculosis clinical isolates using XpertR MTB/RIF in Kampala, Uganda: a retrospective study. BMC Infect Dis 14: 481

85. Comas I, Borrell S, Roetzer A, Rose G, Malla B, et al. (2012). Whole-genome sequencing of rifampicin-resistant Mycobacterium tuberculosis strains identifies compensatory mutations in RNA polymerase genes. Nat Genet 44: 106-110.

86. Brandis G, Hughes D (2013) Genetic characterization of compensatory evolution in strains carrying rpoB Ser531Leu, the rifampicin resistance mutation most frequently found in clinical isolates. J Antimicrob Chemother 68: 2493-2497.

87. Xu Y, Jia H, Huang H, Sun Z, Zhang Z (2015) Mutations found in embCAB, embR, and ubiA genes of ethambutol-sensitive and resistant Mycobacterium tuberculosis clinical isolates from China. BioMed Res Int 2015: 8.

88. Shen X, Shen GM, Wu J, Gui XH, Li X, et al. (2007) Association between embB codon 306 mutations and drug resistance in Mycobacterium tuberculosis. Antimicrob Agents Chemother 51: 2618-2620.

89. Perdigao J, Macedo R, Ribeiro A, Brum L, Portugal I (2009) Genetic characterisation of the ethambutol resistance-determining region in Mycobacterium tuberculosis: prevalence and significance of embB306 mutations. Int J Antimicrob Agent 33: 334-338.

90. Zhang Z, Wang Y, Pang Y, Kam KM (2014) Ethambutol resistance as determined by broth dilution method correlates better than sequencing results with embB mutations in multidrug-resistant Mycobacterium tuberculosis isolates. J Clin Microbiol 52: 638-641.

91. Brossier F, Sougakoff W, Bernard C, Petrou M, Adeyema K, et al. (2015) Molecular analysis of the embCAB locus and embR gene involved in ethambutol resistance in clinical isolates of Mycobacterium tuberculosis in France. Antimicrob Agents Chemother 59: 4800-4808.

92. Tyre GJ, Lew MH, Choong YS, Lim TS, Sarmiento ME, et al. (2015) Vaccines for TB: lessons from the past translating into future potentials. J Immunol Res 2015: 916780.

93. Shi W, Zhang X, Jiang X, Yuan H, Lee JS, et al. (2011a) Pyrazinamide inhibits trans-translation in Mycobacterium tuberculosis. Science 333: 1630-1632.

94. Safi H, Lingaraju S, Amin A, Kim S, Jones M, et al. (2013) Evolution of high-level ethambutol-resistant tuberculosis through interacting mutations in decaprenylphosphoryl-[beta]-D-arabinose biosynthetic and utilization pathway genes. Nat Genet 45: 1190-1197.

95. Schmitt EK, Riwanto M, Sambandamurthy V, Roggo S, Miault C, et al. (2011) The natural product cyclomarin kills Mycobacterium tuberculosis by targeting the ClpC1 subunit of the caseinolytic protease. Angew Chem Int Ed Engl 50: 5889-5891.

96. Liu W, Chen J, Shen Y, Jin J, Wu J, et al. (2017) Phenotypic and genotypic characterization of pyrazinamide resistance among multidrug-resistant Mycobacterium tuberculosis clinical isolates in Hangzhou, China. Clin Microbiol Infect 24: 1016.

97. Jureen P, Werngren J, Toro JC, Hoffner S (2008) Pyrazinamide resistance and pncA gene mutations in Mycobacterium tuberculosis. Antimicrob Agents Chemother 52: 1852-1854.

98. Kahbazi M, Sarmadian H, Ahmadi A, Didgar F, Sadrnia M, et al. (2018) Novel mutations in pncA gene of pyrazinamide resistant clinical isolates of Mycobacterium tuberculosis. Sci Pharm 86: 15.

99. Finken M, Kirschner P, Meier A, Wrede A, Böttger EC (1993) Molecular basis of streptomycin resistance in Mycobacterium tuberculosis: alterations of the ribosomal protein S12 gene and point mutations within a functional 16S ribosomal RNA pseudoknot. Mol Microbiol 9: 1239-1246.

100. Perdigao J, Macedo R, Machado D, Silva C, Jordão L, et al. (2014) GidB mutation as a phylogenetic marker for Q1 cluster Mycobacterium tuberculosis isolates and intermediate-level streptomycin resistance determinant in Lisbon, Portugal. Clin Microbiol Infect 20: 278-284.

101. Sreevatsan SX, Pan KE, Stockbauer DL, Williams BN, Kreiswirth JM (1996) Characterization of rpsL and rrs mutations in streptomycin-resistant Mycobacterium tuberculosis isolates from diverse geographic localities. Antimicrob Agents Chemother 40: 1024-1026.

102. Caceres NE, Harris NB, Wellehan JF, Feng Z, Kapur V, et al. (1997) Overexpression of the D-alanine racemase gene confers resistance to D-cycloserine in Mycobacterium smegmatis. J Bacteriol 179: 5046-5055.

103. Pantel A, Petrella S, Veziris N, Brossier F, Bastian S, et al. (2012) Extending the definition of the GyrB quinolone resistance-determining region in Mycobacterium tuberculosis DNA gyrase for assessing fluoroquinolone resistance in M. tuberculosis. Antimicrob Agents Chemother 56: 1990-1996.

104. Nosova EY, Bukatina AA, Isaeva YD, Makarova MV, Galkina KY, et al. (2013) Analysis of mutations in the gyrA and gyrB genes and their association with the resistance of Mycobacterium tuberculosis to levofloxacin, moxifloxacin and gatifloxacin. J Med Microbiol 62: 108-113.

105. Li J, Gao X, Luo T, Wu J, Sun G, et al. (2014) Association of gyrA/B mutations and resistance levels to fluoroquinolones in clinical isolates of Mycobacterium tuberculosis. Emerg Microbes Infect 3: e19.

106. Cui Z, Wang J, Lu J, Huang X, Hu Z (2011). Association of mutation patterns in gyrA/B genes and ofloxacin resistance levels in Mycobacterium tuberculosis isolates from East China in 2009. BMC Infect Dis 11: 78.

107. Long Q, Li W, Du Q, Fu Y, Liang Q, et al. (2012) gyrA/B fluoroquinolone resistance allele profiles amongst Mycobacterium tuberculosis isolates from mainland China. Int J Antimicrob Agent 39: 486-489.

108. Ajbani K, Rodrigues C, Shenai S, Mehta A (2011) Mutation detection and accurate diagnosis of extensively drug-resistant tuberculosis: report from a tertiary care center in India. J Clin Microbiol 49: 1588-1590.

109. Yuan X, Zhang T, Kawakami K, Zhu J, Li H, et al. (2012) Molecular characterization of multidrug and extensively drug-resistant Mycobacterium tuberculosis strains in Jiangxi, China. J Clin Microbiol 50: 2404-2413.

110. Du Q, Dai G, Long Q, Yu X, Dong L, et al. (2013). Mycobacterium tuberculosis rrs A1401G mutation correlates with highlevel resistance to kanamycin, amikacin, and capreomycin in clinical isolates from mainland China. Diagn Microbiol Infect Dis 77: 138-142.

111. Sowajassatakul A, Prammananan T, Chaiprasert A, Phunpruch S (2014) Molecular characterization of amikacin, kanamycin and Capreomycin resistance in M/XDR-TB strains isolated in Thailand. BMC Microbiol 14: 165.

112. Islam MM, Hameed HM, Mugweru J, Chhotaray C, Wang C, et al. (2017) Drug resistance mechanisms and novel drug targets for tuberculosis therapy. J Genet Genom 44: 21-37.

113. Almeida D, Ioerger T, Tyagi S, Li SY, Mdluli K, et al. (2016) Mutations in pepQ confer low-level resistance to Bedaquiline and Clofazimine in Mycobacterium tuberculosis. Antimicrob Agents Chemother 60: 4590-4599.

114. Shimokawa Y, Sasahara K, Yoda N, Mizuno K, Umehara K (2014) Delamanid does not inhibit or induce cytochrome p450 enzymes in vitro. Biol Pharm Bull 37: 1727-1735.

115. Grzegorzewicz AE, Korduláková J, Jones V, Born SE, Belardinelli JM, et al. (2012) A common mechanism of inhibition of the Mycobacterium tuberculosis mycolic acid biosynthetic pathway by isoxyl and thiacetazone. J Biol Chem 287: 38434-38441.

116. Jia L, Coward L, Gorman GS, Noker PE, Tomaszewski JE (2005) Pharmacoproteomic effects of isoniazid, ethambutol, and N-geranyl- N ' -(2-adamantyl) ethane-1, 2-diamine (SQ109) on Mycobacterium tuberculosis H37Rv. J Pharm Exp Ther 315: 905-911.

117. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, et al. (2009). Treatment outcomes among patients with multidrug-resistant tuberculosis. Lancet Infect Dis 9: 153-161.

118. https://www.cabdirect.org/cabdirect/abstract/20123343939

119. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox HS, et al. (2013) Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J 42: 156-168.

120. Lange C, Abubakar I, Alffenaar JC, Bothamley G, Caminero JA, et al. (2014) Management of patients with multidrug-resistant/ extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. Eur Respir J 44: 23-63.

121. Diacon AH, Dawson R, Von Groote-Bidlingmaier F, Symons G, Venter A, et al. (2012) 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. Lancet 80: 986-993.

122. Lee M, Lee J, Carroll MW, Choi H, Min S, et al. (2012) Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 367: 1508-1518.

123. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, et al. (2013) Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J 41: 1393-1400.

124. Diacon AH, Pym A, Grobusch MP, De los Rios JM, Gotuzzo E, et al. (2014) Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 371: 723-732.

125. Guglielmetti L, Le Du D, Jachym M, Henry B, Martin D, et al. (2015) Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect Dis 60: 188-194.

126. Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB (2010) Treatment outcomes among patients with extensively drug-resistant tuberculosis. Clin Infect Dis 51: 6-14.

127. Tang S, Yao L, Hao X, Zhang X, Liu G, et al. (2015) Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 45: 161-70.