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RECENT ADVANCEMENTS IN THE MANAGEMENT OF MULTI DRUG RESISTANT TUBERCULOSIS (MDR TB)

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Abstract:

Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem, with most cases arising from a blend of physician error and patient non-cooperation during treatment of susceptible TB. The extent and burden of MDR-TB varies significantly from country to country and region to region. There are many drugs available to treat tuberculosis like first line drugs and second line drugs. Even though the number of TB case is increasing day by day. This review is dealing with the FDA approved drugs and drugs under study.

Key Words: *TB, MDR TB, First line drugs, Second line drugs, FDA approved drugs, drugs under study*

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INTRODUCTION:

Tuberculosis (TB) is an infection caused by bacteria *Mycobacterium tuberculosis* (MTB). Usually it affects on the lungs, it can also effects on other parts of the body. TB is spread from one person to other through air. The common symptoms of TB include persistent cough, constant fatigue, loss of appetite, coughing up blood, fever, night sweats, weight loss etc. People at highest risk for developing TB are immune compromised individuals.[1] Which include babies and young children whose immune system have not matured, person with HIV/AIDS, kidney disease or diabetes, organ transplant recipients, cancer patients and person receiving treatment for autoimmune diseases. TB can be classified into two – latent and active. In latent TB the bacteria remain in the body in an inactive state and in active TB the bacteria do cause symptoms. The most common diagnostic test for TB is skin test. Besides this other tests like blood tests, chest X-rays and sputum tests can be used. Now there is an advanced test to detect TB called Xpert *Mycobacterium tuberculosis* / Rifampicin (MTB/RIF). It is a cartridge based automated diagnostic test that can identify *Mycobacterium tuberculosis* DNA and resistance to rifampicin by nucleic acid amplification technique. TB is curable and preventable.[2]

TB can be treated effectively by using first line drugs like Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA), Ethambutol (EMB) and Streptomycin (SM). However this first line therapy often fails to cure TB. At that time, physicians may move to second line drugs. It can be subdivided into two – Fluoroquinolones and Injectable antituberculosis drugs. Fluoroquinolones include Ofloxacin (OFX), Levofloxacin (LEV), Moxifloxacin (MOX) and Ciprofloxacin (CIP). Injectable anti TB drugs include Kanamycin (KAN), Amikacin (AMK) and Capreomycin (CAP).Among these drugs Moxifloxacin, Levofloxacin, Ofloxacin, Amikacin and Kanamycin are not approved by FDA for the treatment of TB.[3]

The greater challenges in TB are multi drug resistant tuberculosis (MDR TB), pediatric TB and TB in association with AIDS. MDR TB is defined as resistance to Isoniazid and Rifampicin. This review is an attempt has been made to elaborate about MDR TB and its management.

Tuberculosis

Tuberculosis (TB) is a bacterial infection that can affect almost any part of the body but is mainly on the lungs. The word tuberculosis was derived from two Latin words – "Tubercle" (Round nodule / Swelling) and "Osis" (Condition). The main causative organism is *Mycobacterium tuberculosis*. Other causative agents include *Mycobacterium africanum*, *Mycobacterium microti* etc. *Mycobacterium tuberculosis* is a gram positive, non spore forming, obligate aerobic, non motile and rod shaped bacteria. The size of the bacteria is 0.2 – 0.6 x 2 – 4µm$^{2.}$ Lipid rich cell wall contains mycolic acid. Hence they are resistant to detergents and antibacterial.[4]

It is a bacterial infection and spread from person to person through air. The common symptoms of TB include persistent chronic cough with or without blood, shortness of breath, chest pain, fatigue, fever, loss of appetite, malaise, night sweating, weight loss, chest pain etc. TB is fatal if it is not detected and treated timely.[5]

Multi drug resistant / Rifampicin resistant TB (MDR/RR-TB) and extensively drug resistant TB (XDR-TB) means that most anti-TB medicines have been used for decades, and resistance to them is widespread. TB strains that are resistant to at least one anti-TB medicine have been reported in every country surveyed. Rifampicin-resistant tuberculosis is caused by bacteria that do not respond to rifampicin, one of the most powerful anti-TB medicines. These patients require MDR-TB treatment. MDR-TB is caused by bacteria that do not respond to at least isoniazid and rifampicin, the two most powerful anti-TB medicines. Patients with MDR/RR-TB require treatment with second line treatment regimens, which are more complex than those used to treat patients without drug-resistant TB. XDR-TB is a form of MDR-TB which is also resistant to two groups of second line anti-TB medicines, making it more difficult to treat.[6]

Global burden

According to the World Health Organization (WHO), tuberculosis (TB) is the leading cause of death attributed to a single microbial pathogen worldwide. A systematic study done by World Health Organization (WHO) in the early 1990s estimated that there were about 8 million TB cases in 1990 and 2.6 to 2.9 million deaths. An outbreak in Spain between 1991 and 1995 killed 47 of 48 patients infected, and in two outbreaks in London the mortality was over 50% in HIV-positive patients. A second major reassessment by WHO was published in 1999 with an estimated 8 million incident cases and 1.9 million TB deaths. In 2011, there were an estimated 8.7 million incidence cases of TB globally. In 2017, an estimated 10 million incident TB cases

and 1.6 million TB deaths occurred, representing reduction of 1.8% and 3.9% from 2016.[7]

MDR TB is a growing challenge worldwide, and an obstacle to TB elimination. Inappropriate treatment leads to drug-resistant TB cases, with an estimated 4,80,000 new cases of drug-resistant TB reported in 2015. The anti-TB drug resistance surveillance data show that 4.1% of new and 19% of previously treated TB cases in the world is estimated to have rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB). In 2016, an estimated 6,00,000 new cases of MDR/RR-TB emerged globally. MDR/RR-TB caused 2,40,000 deaths in 2016. Most cases and deaths occurred in Asia. About 6.2% of MDR-TB cases have additional drug-resistance called extensively drug-resistant TB (XDR-TB).[7]

In 2017, the World Health Organization estimated that 5,58,000 individuals developed multidrug-resistant tuberculosis (MDR-TB).During the past 5 years, MDR-TB has increased by more than 20% annually.[8]

In 2017, 24% of new and70% of previously treated TB patients notified globally were tested for MDR / RR TB (up from 12% and 53% respectively in 2015). In many countries a steady increase has occurred in recent years, driven by the continued expansion in the use of rapid molecular tests. In spite of increased testing the number of MDR / RR TB cases detected in 2017 only reached 161000, a slight increase from the 153000 cases reported in 2016. In 2017, 11000 cases of XDR TB were reported by 77 countries.[9]

Specialised centres in USA have suggested that surgical resection under drug cover is an option in selected cases, particularly those with unilateral disease. Their experience with this approach, coupled with the availability and use of fluoroquinolones, particularly moxifloxacin and levofloxacin, in the drug regimen, has improved the survival in such patients. The long term success rate was increased from 56% in the prior cohort to 75% and the TB death rate fell from 22% to 12% as quinolones were used increasingly. However, these outcomes are still significantly worse than for unselected TB, which is largely fully drug susceptible and for which death rates of 5% and cure rates of 89% for respiratory diseases and 94.4% for all forms of disease in programme conditions are reported.[10]

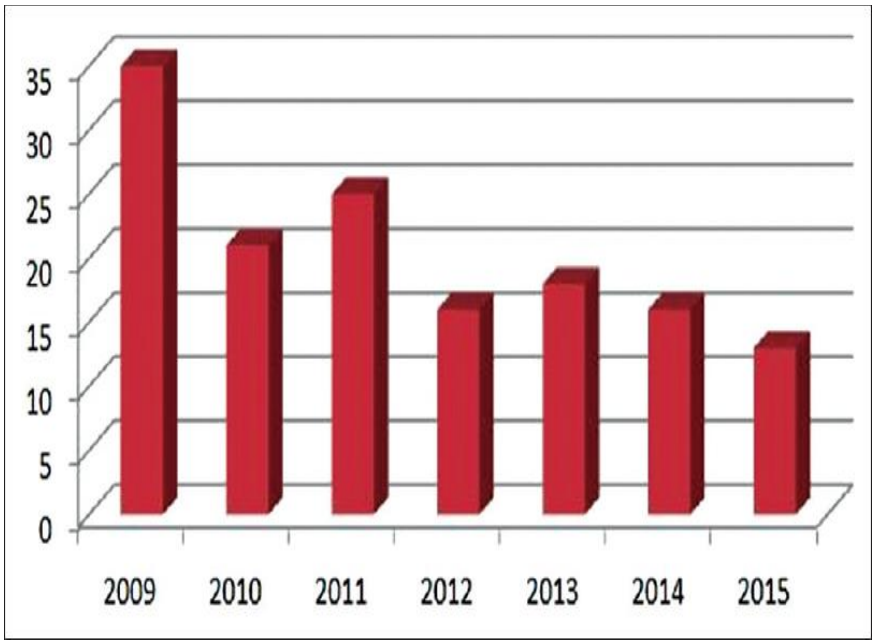


Figure 1.Prevalence of multidrug-resistant-tuberculosis in India year wise

Previous drug treatment is the largest single risk factor for the presence of MDR-TB. Therefore physicians should suspect that any patient with a prior treatment history, or failure during treatment, could have acquired resistance.

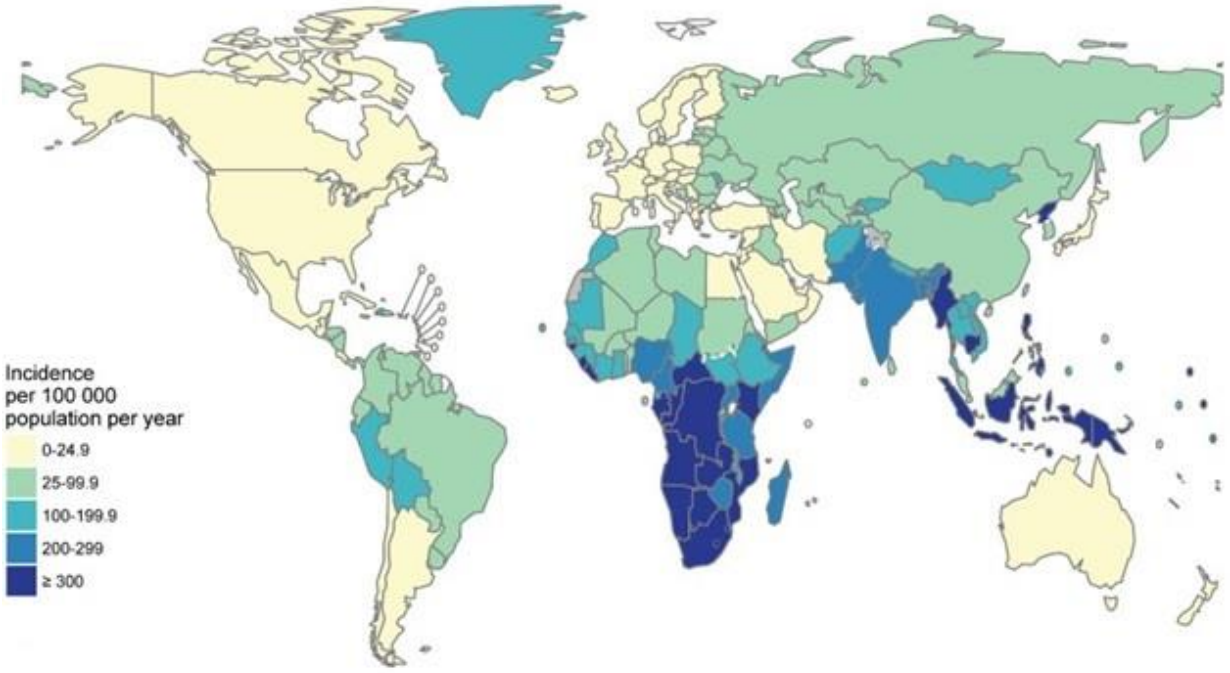


Figure 2.Global coverage of surveillance data on drug resistance, 1995–2017.[7]

In USA, HIV-positive MDR-TB cases initially had 100% mortality, but with greater awareness and earlier diagnosis an improvement in initial survival rates to up to 50% has been reported. HIV-negative cases in the USA have had better response rates of between 56% and 69%.[11]

Diagnosis

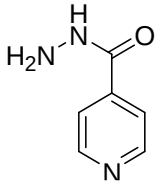
The commonly used diagnostic techniques are:

1. Bacteriological test
2. Sputum culture test
3. Chest X-Ray
4. Tuberculin skin test
5. Nucleic acid amplification (Xpert MTB / RIF).[12]

DRUGS USED TO TREAT IN TB

First line drugs for TB

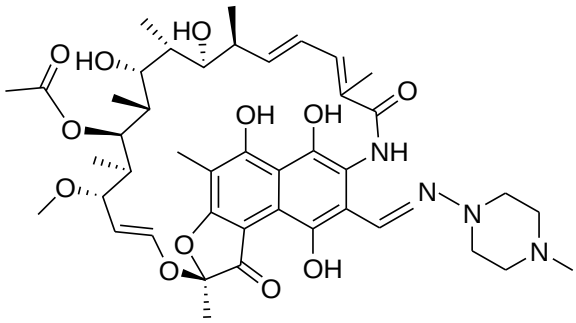
1. Isoniazid



Mechanism of action:

It is a prodrug that inhibits the formation of the mycobacterial cell wall. It must be activated by a bacterial catalase peroxidase enzyme in *Mycobacterium tuberculosis* called KatG. KatG catalyses the formation of isonicotinic acyl radical, which spontaneously couples with NADH to form nicotinoyl – NAD adducts. This complex binds tightly to the enoyl – acyl carrier protein reductase. Thereby blocking the natural enoyl substrate and the action of fatty acid synthase get inhibited. This process inhibits the synthesis of mycolic acids, which are required components of the mycobacterial cell wall. A range of radicals are produced by KatG activation of isoniazid, including nitric oxide.[13]

2. Rifampicin

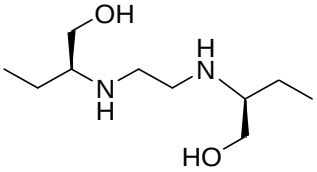


Mechanism of action:

Rifampicin inhibits bacterial DNA dependent RNA synthesis by inhibiting bacterial DNA dependent RNA polymerase. Rifampicin binds to the pocket of the RNA polymerase beta subunit within the DNA / RNA channel, but away from the active site. The inhibitor prevents RNA synthesis by physically

blocking elongation, and thus preventing synthesis of host bacterial proteins.[14]

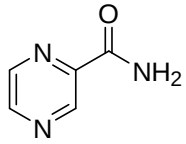
3. Ethambutol



Mechanism of action:

It is bacteriostatic against actively growing TB bacilli. It works by obstructing the formation of cell wall. Mycolic acids attach to the 5'- hydroxyl groups of D- arabinose residues of arabinoglycan and form mycolyl arabinogalactan - peptidoglycan complex in the cell wall. It disrupts arabinogalactan synthesis by inhibiting enzyme arabinosyl transferase. It inhibits the formation of this complex and leads to increased permeability of the cell wall.[15]

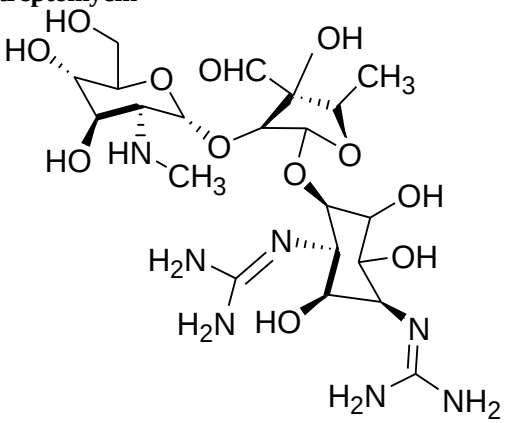
4. Pyrazinamide



Mechanism of action:

It is a prodrugs that stops the growth of *M. tuberculosis*. It diffuses into the granuloma of bacteria where the TB enzyme pyrazinamidase converts pyrazinamide to pyrazinoic acid. Under acidic condition the pyrazinoic acid leaks out and converted into protonated conjugate acid, which diffuse easily back into the bacilli and accumulate. Pyrazinoic acid inhibits the enzyme fatty acid synthase I, which is required for the fatty acid synthesis of bacteria.[16]

5. Streptomycin

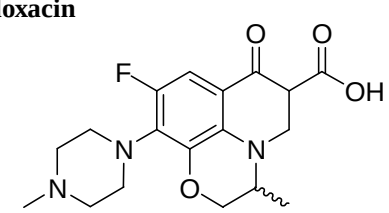


Mechanism of action:

It binds to small 16SrRNA of the 30S subunit of the bacterial ribosome, interfering with the binding of formyl methionyl t RNA to the 30S subunit. This leads to codon misreading, inhibition of protein synthesis and ultimately the death of the microorganism.[17]

Second line drugs for TB

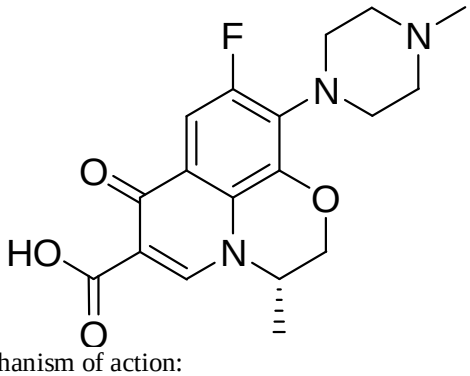
1. Ofloxacin



Mechanism of action:

It is a broad spectrum antibiotic and it functions by inhibiting two bacterial type II topoisomerases, DNA gyrase and topoisomerase IV. Topoisomerase IV is an enzyme necessary for separating the two replicated DNA strands. As a result bacterial cell division inhibited. DNA gyrase is responsible for the super coiling of DNA.[18]

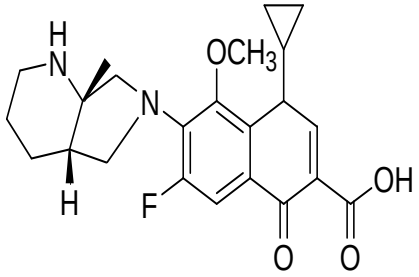
2. Levofloxacin



Mechanism of action:

It is a broad spectrum antibiotic and it functions by inhibiting two bacterial type II topoisomerases, DNA gyrase and topoisomerase IV. Topoisomerase IV is an enzyme necessary for separating the two replicated DNA strands. As a result bacterial cell division inhibited. DNA gyrase is responsible for the super coiling of DNA .[19]

3. Moxifloxacin

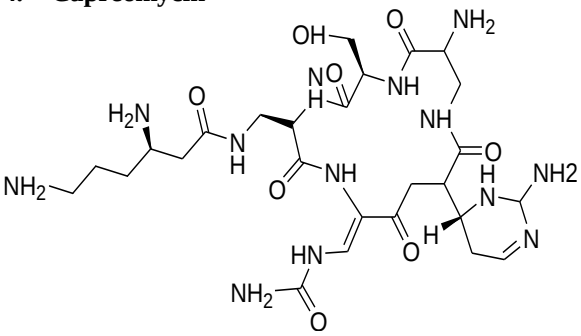


Mechanism of action:

It is a broad-spectrum antibiotic and it functions by inhibiting two bacterial type II topoisomerases, DNA gyrase and topoisomerase IV. Topoisomerase IV is an enzyme necessary for separating the two

replicated DNA strands. As a result bacterial cell division inhibited.[20]

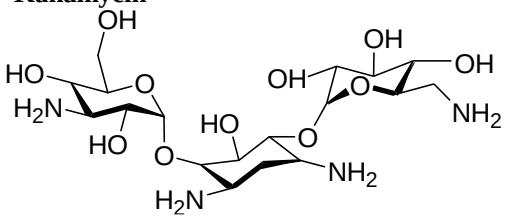
4. Capreomycin



Mechanism of action:

Exact mechanism is not known. It is thought to inhibit protein synthesis by binding to the 70S subunit of ribosome.[21]

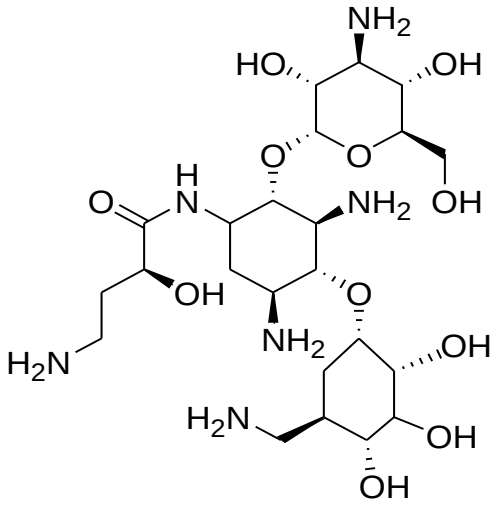
5. Kanamycin



Mechanism of action:

It acts by binding to the 30S subunit of ribosome. As a result alignment in mRNA become incorrect and leads to misreading. Thus wrong amino acids placed into the peptide chain.[22]

6. Amikacin



Mechanism of action:

It binds irreversibly to 16SrRNA and the RNA binding S12 protein of the 30S subunit of ribosome. So that the protein synthesis is inhibited by the change in the shape of ribosome.[23]

The **resistance to atleast Isoniazid and Rifampicin** is called Multi Drug Resistance (**MDR**).

MECHANISM OF RESISTANCE

Isoniazid

Resistance of INH takes place either due to mutation in mycolic acid synthesis or loss of catalase / peroxidase.

Rifampicin

Resistance to rifampicin arises from mutations that alter residues of the rifampicin binding site on RNA polymerase, resulting in decreased affinity for rifampicin or reduced cell wall permeability.[24]

Reasons for the drug resistance

*Clinical / Operational factors

- Unreliable treatment regimen by doctors like lesser number of drugs, indequate dosage / duration
- Addition of a single drug in failing regimen
- Easy availability of drugs in private sector
- Poor drug supply
- Poor bioavailability

*Biological factors

- Initial bacillary population
- Local factors in host favourable for multiplication of bacilli
- Presence of drug in sufficient concentration

*Sociological factors

- Irregular intake
- Inadequate duration
- Neglect of disease
- Ignorance.[24]

Treatment principles of MDR TB

1. Use at least 4 reliable drugs
2. Do not use drugs with cross resistance
3. Eliminate drugs that are not safe for the patient
4. Include drugs from Groups A – C in a heirarcheal order
5. Monitor and manage adverse effects of drugs
6. Never add a single drug to fail regimen.[25]

MDR TB drugs

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens[26]

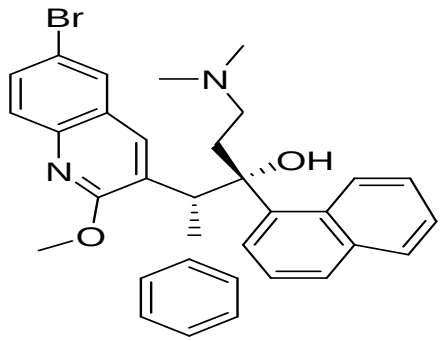
GROUP	MEDICINE	ABBREVIATION
Group A: Include all three medicines (unless they cannot be used) Group B: Add both medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups Aand B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin OR Meropenem	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

The currently recommended short course (9 month) treatment regimen for MDR-TB is preferred in most low- income countries. Commonly prescribed short-course MDR-TB regimens include - Prothionamide or Ethionamide / high dose Isoniazid / Clofazimine / Pyrazinamide / Ethambutol and Moxiflofloxacin in combination with either Kanamycin or Bedaquiline.

FDA approved drugs

A diaryl quinoline compound called Bedaquiline is active against drug-sensitive and drug resistant strains of *M. tuberculosis* in pre-clinical evaluations. The published results of a phase IIb clinical trial with bedaquiline shows that it is an add to MDR-TB backbone treatment regimen. The studies showed significant improvement in the rate of culture conversion by 2 months. Since December 31, 2012, bedaquiline has been approved for use in the USA. On December 19, 2013, the EMA has adopted a positive opinion, recommending granting a conditional marketing authorization for bedaquiline for the treatment of MDR/XDR-TB. [27]

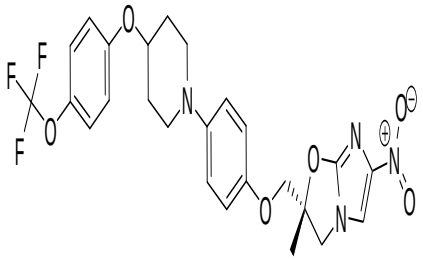
Bedaquiline inhibits the proton pump ATP synthase of *M. tuberculosis.* Due to the lack of ATP bacterial growth arrests within hours.[28]



Bedaquiline

Major side effects of bedaquiline are QT prolongation and liver dysfunction.[29]

The European Medicines Agency (EMA) recommended conditional marketing authorization for **Delamanid**(DLM) in adults with multidrug-resistant pulmonary tuberculosis without other treatment options because of resistance or tolerability. The EMA considered the data show that the benefits of Delamanid outweigh the risks, but that additional studies were needed on the long-term effectiveness. The trial use in adults with MDR-TB is rapidly evolving, with a focus mainly on the use of novel agent in regimens. Based on Phase IIb data, bedaquiline (BDQ) received accelerated approval from the US Food and Drug Administration in 2012, and Delamanid received conditional approval from the European Medicines Agency in 2014.



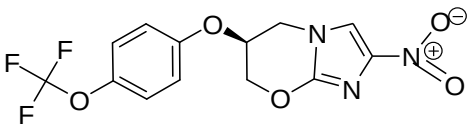
Delamanid

Delamanid is a dihydo nitro imidazoxazole derivative. It acts by inhibiting the synthesis of mycobacterial cell wall components like methoxy mycolic acid and keto mycolic acid.
Major side effect is QT prolongation.[30]

With the availability of new drugs for the treatment of MDR/XDR-TB, the hierarchical order for choosing anti-TB drugs for a MDR/XDR-TB treatment regimen will have to be redefined and updated regularly. At present, the optimal treatment indication and duration of therapy with delamanid or bedaquiline is unclear. It is also unclear whether it is sufficiently safe to use delamanid and bedaquiline together or in combination with moxifloxacin and/or clofazimine in the treatment of MDR/XDR-TB as all of these drugs may lead to an increase in the QT interval with the potential risk of fatal cardiac arrhythmias. While physicians need to be aware of possible potentiating adverse events with new drugs in a combination regimen and are advised to monitor patients closely, new drugs should be available for all patients who would benefit from them in view of the overall limited prognosis in MDR/XDR-TB.[6]

On November 22, 2013, the EMA recommended conditional authorization of delamanid for use in combination with other medicines against MDR/XDR-TB, when an effective treatment regimen cannot otherwise be devised for reasons of resistance or tolerability.

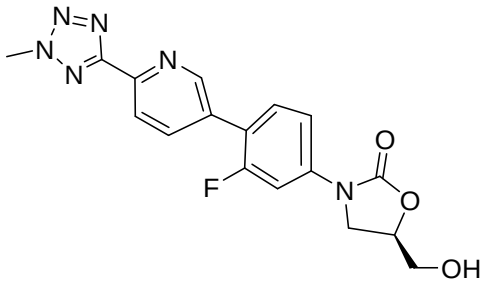
Pretomanid and **Tedizolid** receive further approvals they could be also considered drugs for compassionate use on a similar template/pathway.



Pretomanid

Pretomanid (PA-824) is a bicyclic nitroimidazoleprodrug compound with a complex mechanism of action. It is active against both replicating and hypoxic non replicating Mycobacterium tuberculosis. It shows a mixed effect both on genes responsive to both cell wall inhibition and respiratory poisoning.

The most common side effects include nerve damage, headache, hypoglycemia and liver inflammation.[31]



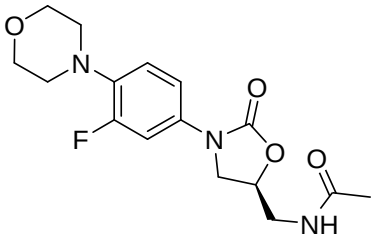
Tedizolid

Tedizolid phosphate is a prodrug activated by plasma or intestinal phosphatases to tedizolid. Tedizolid exerts its bacteriostatic microbial activity through inhibition of protein synthesis by binding to the 50S ribosomal subunit of bacteria.

Common side effects are head ache, vomiting, diarrhea. Phase I studies shows hematologic side effects when exposed to dose more than 6 days.[32]

Drugs under study

New drugs that have been evaluated for the treatment of TB in clinical phase II–III include **Linezolid** and **PA-824 (Pretomanid)**. Of the new compounds, delamanid and PA-824 are two nitro imidazopyrans with encouraging trial results. Delamanid promised a good early bactericidal activity in phase I studies. It also demonstrated efficacy as an add-on to a MDR-TB backbone treatment regimen in one recently published randomized, placebo controlled phase IIb study.

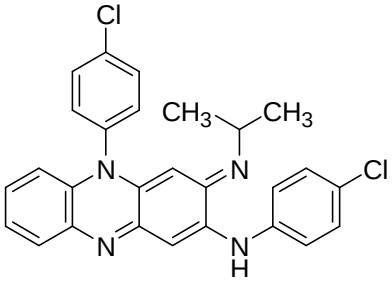


Linezolid

Due to the limited data available on the efficacy and effectiveness of delamanid for the treatment of MDR/XDR-TB at present, the EMA concluded that additional studies on the long-term effectiveness of delamanid should be conducted. In phase II clinical trials, the drug was used in combination with standard treatments, such as four or five of the Ethambutol, Isoniazid, Pyrazinamide, Rifampicin, am inoglycoside antibiotics and quinolones. Healing

rates were significantly better in patients who additionally took Delamanid.

There are at least four open clinical trials, including three phase III trials, analyzing **Clofazimine** in the treatment of MDR-TB. These studies are focused on clofazimine in combination with other TB drugs to produce less toxic and shorter regimens for MDR-TB infections.The adverse effects of clofazimine are relatively minor. The drug commonly causes a reversible orange-brown discoloration of the skin.



Clofazimine

Substitution of a drug in case of additional drug resistance or intolerance can be effected by, in order of preference with linezolid (Lzd), clofazimine (Cfz) or cycloserine (Cs). High-dose isoniazid (15-20 mg/kg/day) may not be useful in Indian patients with Hr-TB since the *kat* G gene mutation conferring high-dose INH resistance is present in >90% of isolates. According to the first National Anti-Tuberculosis Drug Resistance Survey (NDRS) in India, resistance to any fluoroquinolone (FQ) was found in about eight per cent of Hr-TB and resistance to Lzd was uncommon in MDR/RR-TB and even less in mono/poly-DR-TB (personal communication with RNTCP). Cultures should be done at the end of 2-3 months and thereafter as expropriate.

Although **Moxifloxacin** may arguably be more potent than Lfx, the main advantage of the latter is less QT prolongation, which has obvious advantages when combined with other QT prolonging agents, such as bedaquiline (Bdq) and Cfz in regimen. Peak plasma concentration and exposure to Mfx significantly decreases with concurrent administration of rifampicinthis is another advantage of using Lfx, which does not require dosage adjustment. Unlike Mfx, Lfx requires dose modification in patients with advanced stages of chronic kidney disease (CKD).

The recently published consolidated guidelines on MDR/RR-TB are based on evidence synthesized from a recently completed Phase III clinical trial of delamanid (Dlm) an individual patient data meta-analysis (IPD-MA) of longer and 9-12-month shorter MDR-TB regimens and efficacy and pharmacokinetic data from Dlm and Bdq-related clinical trials. There are no changes in the timing of antiretroviral drugs administration in people living with HIV (PLHIV) with MDR/RR-TB, use of surgery and models of MDR-TB care (ambulatory care/hospitalization).

A new feature in the guidelines is that the second-line anti-TB drugs used for designing individualized MDR-TB regimens have been re-grouped into A, B and C and the drug ranking is based on their estimated efficacy profiles. The group A drugs include FQ, Lfx or Mfx; Bdq and Lzd; group B includes Cfz and Cs or terizidone and group C contains ethambutol (E), Dlm, pyrazinamide, imipenem-cilastatin (Imp-Cln) or meropenem (Mpm), amikacin (Am) or streptomycin (S), ethionamide (Eto), or prothionamide and *p*-aminosalicylic acid (PAS). Lack of efficacy in the Dlm phase III study has resulted in its classification as a group C drug though this was based on a six-month culture conversion outcome.

While designing the individualized longer (18-20 month) MDR-TB regimen, a strong recommendation has been made to include all three drugs from group A, and to complete the regimen, the fourth drug should be from group B (and if it is not possible, then the fourth drug may be selected from the group C). A fully oral long-term regimen is the preferred option and the injectable agents, kanamycin and capreomycin, are no longer recommended because these were associated with higher treatment failure, relapse rates and mortality and toxicity. The long-term Bdq-containing drug regimen should have at least four drugs for initial six months and subsequently three drugs to be continued for rest of the duration of treatment. Although the optimal number of drugs for the regimen is uncertain, we recommend a minimum of four but ideally five likely effective drugs. The individualized, longer MDR-TB regimen is to be administered for a total duration of 18-20 months, and the duration is primarily based on patient's response to treatment or 15-17 months after culture conversion. However, the optimal treatment duration remains unclear. The WHO recommendations have emphasized monthly sputum cultures along with smear microscopy.

Pyrazinamide is to be used for MDR/RR-TB only when Drug susceptibility test (DST) reveals susceptibility. Every dose of Imp-Cln or Mpm is administered with clavulanic acid this combination is counted as single drug. In selected patients where a regimen cannot be constructed because of resistance profiles or drug-specific toxicity, Am or streptomycin

is to be used only in patients >18 yr of age, and when high-quality audiometry monitoring for hearing loss is available. Am is to be substituted with streptomycin only if it is not available or some other contraindication exists, and when DST confirms susceptibility to streptomycin.

It should be noted that **Thiacetazone, Gatifloxacin** and **high-dose isoniazid** were not included in the IPD-MA for longer regimens because of an inadequate number of patients. Evidence on the safety and efficacy of the following drugs was insufficient for review: use of Bdq beyond six months and below the age of six years and Dlm use beyond six months and below the age of three years; concomitant use of Bdq and Dlm. It was observed that the use of Lzd for at least six months showed increased efficacy and using it for the entire duration would likely be better however, one needs to balance this against the high rates of drug toxicity with prolonged use.

The new WHO guidelines has left open the option of using the longer 18-20 month group A-based regimen or the standardized shorter MDR-TB regimen containing an injectable which is given for 9-11 months. In the recently published STREAM trial, the shorter injectable containing 9-11 month regimen was found to be non-inferior to the conventional 18-20 month older WHO regimen (also contained an injectable). However, bacteriologic outcomes were worse with the shorter regimen and there was a trend to worse outcomes in HIV-infected persons in both arms. Given these considerations, the toxicity and tolerability profiles , recommendation is that the longer pan oral regimen is preferable and that the standardized shorter MDR-TB regimen containing an injectable should only be used as an exception (for example, if drugs are not readily accessible) and provided (*i*)there is no proven or likely resistance to any component of the regimen (except isoniazid), (*ii*) there is access to baseline and longitudinal monitoring for hearing loss, (*iii*) FQ and second line injectable drug (SLID) resistance has been excluded, and (*iv*) patients have been counseled about the risks of this regimen and agree to receive it. There should be clear plans within the programme or provider setting to transition to an all-oral group A-based regimen because the shorter WHO injectable-based regimen is likely to be an inferior one from an efficacy and mortality point of view (though there are no head-to-head trials yet), and Am is toxic and associated with chronic painful injections driving poor adherence.

Active TB drug-safety monitoring and management (aDSM) should be an integral part of MDR-TB management as several drugs have additive toxicities. Similarly, several drugs (Lzd, ethambutol and INH) in the regimen, when given in combination, can produce optic neuropathy.

Lzd is a potent drug with potential toxicity when used on long-term basis in MDR-TB regimens. Hematological toxicity occurs early, whereas peripheral and optic neuropathy occurs late. Lactic acidosis is a rare complication. Pyridoxine (100 mg daily) can be administered to decrease the risk of hematological toxicity. Lzd is very rarely associated with serotonin syndrome when administered with selective serotonin re-uptake inhibitors and other medicines known to increase serotonin concentration in the central nervous system. In this specific context, patients should be instructed to avoid foods and liquids rich in tyramine concentration.[33]

Table 2.Key Phase II and III trials in adults for the treatment of MDR-TB, with their intervention arm components[34]

Trial name,identifier	Phase	Components of intervention arm/s
NC005: adult subjects with drug-susceptible	II	Pyrazinamide(PZA),Bedaquiline
or pulmonary MDR-TB; NCT02193776		(BDQ), Prothionamide (PTM),
		Moxifloxacin(MFX)
Opti-Q: Efficacy and safety of LVX for the	II	Levofloxacin(LVX)
treatment of MDR-TB;NCT01918397		
STREAM: Evaluation of patients with		
MDR-T/B; NCT02409290	III	Stage 1: high-dose MFX, PZA,
		Ethambutol(EMB), Kanamycin (KM),
		high-dose Isoniazid(INH),Clofazimine
		(CFZ)
		Stage 2: BDQ, CFZ, EMB, PZA,
		LVX, INH, PTM

NIX-TB: subjects with drug resistant		
pulmonary tuberculosis;NCT02333799	III	LZD, BDQ, PTM
STAND: Shortening treatment by		
advancing novel drugs; NCT02342886	III	PZA, MFX, PTM
NEXT-TB: a new treatment regimen		
NCT02454205	II/III	LZD, BDQ, PZA, LVX, ETH/high-dose
		INH/ Tedizolid (TZD)
Trial 213: NCT01424670	III	Delamanid (DLM)
TB-PRACTECAL: NCT02589782	II/III	BDQ, PTM, MFX, LZD, CFZ

Prevention

Infection control measures for MDR/XDR-TB are necessary to prevent transmission of *M. tuberculosis*. CDC and WHO have developed policies and guidelines on TB infection control. When it comes to preventing transmission, there is no essential difference between MDR/ XDR-TB strains and other strains of *M. tuberculosis*. The persons to be protected are household contacts (e.g. family members) and in a hospital setting, other patients, healthcare workers, cleaners, administrative staff, etc., and visitors. The best way to prevent transmission of M. tuberculosis is prompt diagnosis and start of effective treatment.[35]

Contagiousness of the index case can be measured by investigating the sputum acid fast bacilli (AFB) but 15% of transmission in the community comes from sputum AFB smear-negative index cases. There is a wide variability in contagiousness of AFB sputum smear-positive index cases. In general, the duration of contagiousness of patients with MDR/XDR-TB is longer than that of patients with non MDR/XDR-TB.

Individuals suspected of having TB should be separated from other patients and evaluated for TB without waiting. Hospitalization should include airborne isolation precautions and be limited primarily to contagious AFB sputum smear-positive TB patients. Infectiousness is substantially reduced once a patient is on an adequate regimen and it is probably not necessary to keep a patient in hospital until their cultures become negative. In some settings, patients with MDR/XDR-TB are discharged from the hospital after 2 weeks of an adequate treatment, although many centres require a negative result from three sputum cultures collected over a 14-day period in patients with MDR/XDR-TB before they are considered for discharge. At the same time, the optimal time for safe discharge of patients with MDR/XDR-TB is not known.

In daily practice, strict isolation of a patient is often not possible. Smoking is generally forbidden in patient rooms and patients with contagious TB, especially MDR/XDR-TB, should not use shared smoking shelters. If patients are unwilling or unable to stop smoking, they should smoke outside. There must be awareness that in-patients will socialize in the evenings, at nights and on weekends, when infection control measures by hospital staff cannot be strictly enforced.

Any *M. tuberculosis* transmission risk reduction programme should include the issues of administrative and environmental measures and personal respiratory protection. In hospitals specializing in the care of patients with MDR/XDR-TB, *M. tuberculosis* transmission risk assessment should be conducted regularly within a TB infection control plan. In high-risk areas of *M. tuberculosis* transmission, procedures and staff should be identified for personal respiratory protection (e.g. education and training). Respirator fit tests (qualitative or quantitative) should be organised on an annual basis. Hospital staff sharing air with contagious patients with MDR/XDR-TB should be wearing FFP2-certified respirators.

Use of surgical masks by contagious MDR/XDR-TB patients indoors reduces transmission risk by half. Because of the very high air change rate outdoors, any recommendation to use masks for TB patients in the open air is not justified. Natural ventilation should be maximised by appropriate architectural design and rational administrative support. Sustainable environmental controls should be implemented for high-risk areas for TB transmission where administrative controls cannot further substantially reduce the risk. Mechanical ventilation should provide directional airflow, and negative pressure is required in isolation rooms and other high-risk areas. 12 air changes per hour (ACH) are recommended for new facilities, but 6 ACH may be acceptable for older facilities. Contaminated air exhaust outlets should be located 8 m from windows,

air intakes and occupied areas, or effectively decontaminated by in-duct ultraviolet germicidal irrigation (UVGI) or high-efficiency particulate air filtration. Upper room UVGI fixtures, professionally designed, installed and maintained, are an effective and sustainable option for limited-resource settings.

Air recirculation and room air cleaners are not recommended for high *M. tuberculosis* transmission risk areas. To ensure sustainability of engineering controls, their application should be rationally limited to high-risk areas; systems should be professionally designed, installed, commissioned and maintained. As bronchoscopy and endotracheal intubation of patients with pulmonary TB pose a very high risk of transmission for all occupants in the room, a clear protocol of TB hygiene precautions should be available for these interventions in patients with pulmonary TB or those with an unclear diagnosis where pulmonary TB is part of the differential diagnosis. Indications for such procedures should be strictly limited; they should be performed in isolated, ideally negative pressure mechanically ventilated rooms with 12 ACH. All occupants should wear FFP2 or FFP3 respirators. If effective mechanical ventilation is not available, the whole room should receive UVGI after completion of the procedure with sufficient exposure.

To help reduce the risk of contaminating a ventilator or discharging *M. tuberculosis* into the ambient air when mechanically ventilating (i.e. with a ventilator or manual resuscitator) a patient with suspected or confirmed TB, a bacterial filter should be placed in the patient's endotracheal tube (or at the expiratory side of the breathing circuit of a ventilator). In selecting a bacterial filter, preference should be given to models specified by the manufacturer to filter particles 0.2 mm in size in both the unloaded and loaded states with a filter efficiency of 95% (i.e. filter penetration 5%) at the maximum design flow rates of the ventilator for the service life of the filter, as specified by the manufacturer.

Transport of contagious patients inside the hospital should be limited (avoid use of lifts, sitting in waiting areas). Transport of contagious patients outside the hospital should preferably be carried out in vehicles with a separate compartment for the patient and for accompanying persons. If weather permits, open windows allow very high air change rates inside the vehicle. At least a surgical mask or a respirator without an exhalation valve should be worn by the patient, and a FFP2 respirator worn by the driver and accompanying person during the journey. Some of these measures recommended by the international airborne infection control expert community have no solid evidence base and there is still a lot of research to be done in this field.

Some individuals who have not had previous TB treatment are infected by MDR-TB. Many new cases of MDR-TB are created each year by a combination of physician error and poor patient compliance with treatment, which turn fully susceptible organisms, or those with less complex resistance patterns, into MDR-TB. Support and funding of national TB programmes, in which treatment is given as directly observed therapy (DOT), is essential for all persons with TB if at all possible. Physicians should always use evidence-based treatment guidelines and drugs of proven bio-availability. WHO recommend a 6 month initial treatment regimen of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin and isoniazid for 4 months (2RHZE–4RH). If the patient fails treatment (positive cultures or sputum smears in months 5 or 6 of treatment) or relapses, an 8 month retreatment regimen is recommended. This consists of streptomycin, rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin, isoniazid, pyrazinamide and ethambutol for 1 month, followed by rifampicin, isoniazid and ethambutol for 5 months (2SRHZE–1RHZE–5HRE).

CONCLUSION:

Tuberculosis is a bacterial infection. It is fatal if it is not detected and treated timely. The normal pulmonary TB can be treated by using first line drugs for 6 months in a regular manner. For ensuring the regular intake of drug regimen WHO established Directly Observed Treatment (DOTS) therapy. Aserious obstacle in the treatment of TB is drug resistance. The resistance to most effective Isoniazid and Rifampicin is called MDR TB. Resistance developed to second line fluoroquinolones and injectables are called XDR TB. Resistance may arise due to inappropriate medicine usage or bacterial mutation. Thus the treatment of MDR/XDR TB is very difficult. Usually combinations of first and second line drugs are used for a long time upto 9 months for MDR TB. Bidaquiline, Delamanid, Pretomanid and Tedizolid are the FDA approved drugs for MDR TB. The major side effects of these drugs are QT prolongation and liver damages. Hence there is a need to develop effective drugs with least side effect.

REFERENCES:

1. Nath, H. and S. Ryoo (2013). "First–and Second–Line Drugs and Drug Resistance." Tuberculosis-Current Issues in Diagnosis and Management. *InTech*.
2. Sharma, S. K. and K. Dheda (2019). "What is new in the WHO consolidated guidelines on drug-resistant tuberculosis treatment?" *Indian Journal of Medical Research* **149**(3): 309.
3. Jnawali, H. N. and S. Ryoo (2013). First–and second–line drugs and drug resistance. Tuberculosis-Current Issues in Diagnosis and Management, *IntechOpen*.
4. Lange, C., et al. (2014). Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement, *Eur Respiratory Soc*.
5. Ngwira, L.-G., et al. (2018). "Delay in seeking care for tuberculosis symptoms among adults newly diagnosed with HIV in rural Malawi." *The International Journal of Tuberculosis and Lung Disease* **22**(3): 280-286.
6. Lange, C., et al. (2018). "Revising the definition of extensively drug-resistant tuberculosis." *The Lancet Respiratory Medicine* **6**(12): 893-895.
7. Dye, C. (2006). "Global epidemiology of tuberculosis." *The Lancet* **367**(9514): 938-940.
8. Tiberi, S., et al. (2019). "Challenging MDR-TB clinical problems–The case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs." *International Journal of Infectious Diseases* **80**: S68-S72.
9. McNeil, M. B., et al. (2018). "Cell wall inhibitors increase the accumulation of rifampicin in Mycobacterium tuberculosis." *BioRxiv*: 424309.
10. Beavers, S. F., et al. (2018). "Tuberculosis mortality in the United States: epidemiology and prevention opportunities." *Annals of the American Thoracic Society* **15**(6): 683-692.
11. Mukonzo, J., et al. (2019). "Potential drug–drug interactions between antiretroviral therapy and treatment regimens for multi-drug resistant tuberculosis: Implications for HIV care of MDR-TB co-infected individuals." *International Journal of Infectious Diseases* **83**: 98-101.
12. Pooran, A., et al. (2019). "Point of care Xpert MTB/RIF versus smear microscopy for tuberculosis diagnosis in southern African primary care clinics: a multicentre economic evaluation." *The Lancet Global Health* **7**(6): e798-e807.
13. Lei, B., et al. (2000). "Action mechanism of antitubercular isoniazid Activation by Mycobacterium tuberculosis KatG, isolation, and characterization of InhA inhibitor." *Journal of Biological Chemistry* **275**(4): 2520-2526.
14. MacNeil, A., et al. (2019). "Global epidemiology of tuberculosis and progress toward achieving global targets—2017." *Morbidity and Mortality Weekly Report* **68**(11): 263.
15. Pawar, A., et al. (2019). "Ethambutol targets the glutamate racemase of Mycobacterium tuberculosis—an enzyme involved in peptidoglycan biosynthesis." *Applied microbiology and biotechnology* **103**(2): 843-851.
16. Speirs, R., et al. (1995). "Activity of n-propyl pyrazinoate against pyrazinamide-resistant Mycobacterium tuberculosis: investigations into mechanism of action of and mechanism of resistance to pyrazinamide." *Antimicrobial Agents and Chemotherapy* **39**(6): 1269-1271.
17. Dal Molin, M., et al. (2018). "Molecular mechanisms of intrinsic streptomycin resistance in Mycobacterium abscessus." *Antimicrobial Agents and Chemotherapy* **62**(1): e01427-01417.
18. Liu, T., et al. (2019). "New insights into the effect of pH on the mechanism of ofloxacin electrochemical detection in aqueous solution." *Physical Chemistry Chemical Physics* **21**(29): 16282-16287.
19. Davis, R. and H. M. Bryson (1994). "Levofloxacin." *Drugs* **47**(4): 677-700.
20. Blondeau, J. M. (2004). "Fluoroquinolones: mechanism of action, classification, and development of resistance." *Survey of Ophthalmology* **49**(2): S73-S78.
21. Heifets, L., et al. (2005). "Capreomycin is active against non-replicating M. tuberculosis." *Annals of Clinical Microbiology and Antimicrobials* **4**(1): 6.
22. Umezawa, H., et al. (1973). "Kanamycin phosphotransferase I: Mechanism of cross resistance between kanamycin and lividomycin." *The Journal of Antibiotics* **26**(7): 407-411.
23. Alangaden, G. J., et al. (1998). "Mechanism of resistance to amikacin and kanamycin in Mycobacterium tuberculosis." *Antimicrobial Agents and Chemotherapy* **42**(5): 1295-1297.
24. Almeida Da Silva, P. E. and J. C. Palomino (2011). "Molecular basis and mechanisms of drug resistance in Mycobacterium tuberculosis: classical and new drugs." *Journal of Antimicrobial Chemotherapy* **66**(7): 1417-1430.
25. Loveday, M., et al. (2018). "MDR-TB patients in KwaZulu-Natal, South Africa: Cost-effectiveness of 5 models of care." *PloS one* **13**(4): e0196003.
26. Organization, W. H. (2018). Rapid communication: key changes to treatment of multidrug-and rifampicin-resistant tuberculosis (MDR/RR-TB), World Health Organization.
27. Wallach, J. D., et al. (2019). "Timeliness of Postmarket Studies for New Pharmaceuticals Approved Between 2009 and 2012: a Cross-Sectional

Analysis." *Journal of General Internal Medicine* **34**(4): 492-495.
28. Vasava, M. S., et al. (2019). "Development of new drug-regimens against multidrug-resistant tuberculosis." *Indian Journal of Tuberculosis***66**(1): 12-19.
29. Jones, J., et al. (2019). "Adverse drug reactions in South African patients receiving bedaquiline-containing tuberculosis treatment: an evaluation of spontaneously reported cases." *BMC Infectious Diseases* **19**(1): 544.
30. Fujiwara, M., et al. (2018). "Mechanisms of resistance to delamanid, a drug for Mycobacterium tuberculosis." *Tuberculosis* **108**: 186-194.
31. Thompson, A. M., et al. (2017). "Antitubercular nitroimidazoles revisited: synthesis and activity of the authentic 3-nitro isomer of pretomanid." *ACS Medicinal Chemistry Letters* **8**(12): 1275-1280.
32. Zhanel, G. G., et al. (2015). "Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens." *Drugs* **75**(3): 253-270.
33. Millard, J., et al. (2018). "Linezolid pharmacokinetics in MDR-TB: a systematic review, meta-analysis and Monte Carlo simulation." *Journal of Antimicrobial Chemotherapy***73**(7): 1755-1762.
34. Seddon, J. A., et al. (2018). "Conducting efficacy trials in children with MDR-TB: what is the rationale and how should they be done?" *The International Journal of Tuberculosis and Lung Disease***22**(5): S24-S33.
35. Ormerod, L. P. (2005). "Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment." *British medical bulletin* **73**(1): 17-24.