IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

ADVANCES IN THE DIAGNOSIS OF TUBERCULOSIS

[1]Nandini V. Pawar, [2]Lalita K. Dahiwade, [3]Kavita A. Nangare [4]Santosh A. Payghan
[1]Student, [2]Assistant Professor, [3]Assistant Professor, [4]Principal
[2]Department of Pharmaceutical Chemistry,
Vasantidevi Patil Institute of Pharmacy, Kodoli,
Tal. Panhala, Dist. Kolhapur (MS) Pin Code- 416114

Abstract: This article reviews the published literature on tuberculosis is one among the foremost ancient diseases of mankind, with molecular evidence going back to over 17,000 years. In spite of newer modalities for diagnosis and treatment of TB, unfortunately, people are still suffering, and worldwide it's among the highest 10 killer infectious diseases, second only to HIV. Consistent with World Health Organization (WHO), TB may be a worldwide pandemic. It's a number one explanation for death among HIV-infected people. In India, historically speaking, fight against TB are often broadly classified into three periods: early period, before the discoveries of x-ray and chemotherapy; post-independence period, during which nationwide TB control programs were initiated and implemented; and therefore the current period, during which the continued WHO-assisted TB control program is in situ . Today, India's DOTS (directly observed treatment-short course) program is that the fastest-expanding and therefore the largest program within the world in terms of patients initiated on treatment; and the second largest, in terms of population coverage.

Index Terms - Tuberculosis, diagnosis, Mycolic acid.

INTRODUCTION:

Tuberculosis is that the leading infectious explanation for death worldwide. An estimated 3 million people with active tuberculosis were either not diagnosed or were diagnosed but not notified through national reporting systems in 2019. The so-called missing many people with undiagnosed or untreated active tuberculosis are in danger of death and severe illness, and may transmit tuberculosis to others in their households and communities. Declines in global tuberculosis incidence are slow and, at the speed of current progress, are unlikely to satisfy the WHO End TB Strategy targets to scale back incidence by 90% and tuberculosis deaths by 95% by 2035. Therefore, implementations of effective, evidence-based strategies which will increase diagnosis and treatment of tuberculosis, and potentially reduce tuberculosis transmission, are urgently required. Because tuberculosis care and prevention interventions that rely totally on passive case detection and health facility-based screening strategies have insufficiently reduced tuberculosis incidence, many national tuberculosis programs have promoted community-based active case-finding interventions.

Health planners and national tuberculosis programmes should consider the implementation of active case-finding for tuberculosis interventions as a part of neat research protocols in urban populations with a high prevalence of undiagnosed tuberculosis and in other populations, to contribute evidence to outstanding knowledge gaps. It was further reported that around 1.3 million patients succumbed almost every year thanks to Tuberculosis. Treatment of TB is even more difficult and challenging with the emergence of drug-resistant variants of tubercle bacillus. In 2012, about 45,000 cases of MDR-TB were identified and an estimated 170,000 casualties occurred because of TB. The condition of MDR-TB becomes worse when Mycobacterium strain gains resistance to more drugs. Emergence of resistance strains to commonly used anti-TB drugs has caused dilemma to researchers. Among all the infectious diseases, tuberculosis reports the very best death rate worldwide exceeding HIV/AIDS. Mycobacterium genome possessing mutation and other structural changes can evade the drugs commonly wont to inhibit them. The outbreak of resistance made the control measures and drugs of the disease more complicated, especially when the patient is co-infected with HIV virus. 65 countries have initiated tuberculosis prevention in people living with HIV, of who account for nearly 9% of all cases and 1.8 million people with tuberculosis. The general coverage in 66 countries was 49%, which looks promising to realize the target of 6 million people over 2018–22. Yet, the amount of household contacts had a way smaller coverage, for instance, only 27% of all the estimated 1.3 million eligible children younger than 5 years.

COMMON SYMPTOMS OF TB:

Two screening tools, namely symptom elicitation and chest radiography, are generally utilized in community based TB disease prevalence surveys. In such surveys, the utilization of chest radiography as a screening tool is challenging thanks to the common non-availability of mobile X-ray units. The value of X-ray films and therefore their processing and the requirement of two independent readers, also make the utilization of this tool a challenge in such surveys. Symptom elicitation may be a relatively simple and cheap screening tool. It's also rapid, also as cost-effective. A study conducted by the National Institute for Research in Tuberculosis, Chennai has shown that in surveys conducted in India about two thirds of cases are picked up by symptom screening alone, which the entire prevalence are often estimated by applying a

correction factor of 1.7.2 within the present study, we used symptom elicitation alone, administered by trained field workers, because the screening tool for the detection of cases. To make sure quality, a supervisor independently interviewed 10% of the adults previously screened by the sector workers for symptoms. The findings of this study reconfirm the importance of cough because the predominant symptom of TB disease in screened populations. Cough, with or without other symptoms, was present in 75% of the symptomatic individuals and in 88% of the entire PTB cases detected within the survey. Similar findings are reported in other surveys that used symptoms for screening the population. The elicitation of a previous history of treatment during symptom inquiry yielded 5.9% cases within the present study. Pain was subsequent most common symptom being present in 996 (13.5%) of symptomatic individuals, and contributing 4.5% of the entire cases detected. The elicitation of either of the two symptoms of cough and pain, and/or a history of previous treatment, led to the identification of 95% of the total symptomatic individuals and detection of just about 99% of the total smear positive PTB cases detected within the survey. The contribution of a history of fever alone (without cough and chest pain) in identifying symptomatic individuals was negligible (3.1%) and yielded no sputum positive cases. Similar findings have also been reported by other workers. This suggests that a history of fever alone could also be safely excluded from the symptoms to be elicited in future community surveys, with none appreciable impact on the amount of symptomatic and PTB cases detected. The workload and therefore the cost involved in collection and processing of sputum samples also can be reduced as a result.

TYPES OF TB INFECTION:

1. **Multidrug-Resistant Tuberculosis (MDR-TB):**

Multidrug-resistant tuberculosis (MDR-TB) caused by tubercle bacillus that's immune to both isoniazid and rifampicin with or without resistance to other drugs, may be a phenomenon that's threatening to destabilize global tuberculosis (TB) control. MDR-TB may be a worldwide problem, being present virtually altogether countries that were surveyed. Consistent with current World Health Organization and therefore the International Union against Tuberculosis and Lung Disease estimates, the median prevalence of MDR-TB has been 1.1% in newly diagnosed patients. The proportion, however, is considerably higher (median prevalence, 7%) in patients who have previously received anti-TB treatment. While host genetic factors may contribute to the event of MDR-TB, incomplete and inadequate treatment is that the most vital factor resulting in its development, suggesting that it's often a man-made tragedy. Efficiently run TB control programs supported a policy of directly observed treatment, short course (DOTS), are essential for preventing the emergence of MDR-TB. The management of MDR-TB may be a challenge that ought to be undertaken by experienced clinicians at centers equipped with reliable laboratory services for mycobacterial cultures and in vitro sensitivity testing because it the requires prolonged use of costly second-line drugs with a big potential for toxicity. The judicious use of drugs; supervised standardized treatment; focused clinical, radiologic, and bacteriologic follow-up; and surgery at the acceptable juncture are key factors within the successful management of those patients. With newer effective anti-TB drugs still a foreign dream, innovative approaches like DOTS-Plus are showing promise for the management of patients with MDR-TB under program conditions and appear to be a hope for future. Errors in TB management like the utilization of single drug to treat TB, the addition of one drug to a failing regimen, the failure to spot preexisting resistance, the initiation of an inadequate primary regimen, the failure to spot and address non-adherence to treatment, inappropriate isoniazid preventive therapy, and variations within the bioavailability of anti-TB drugs predispose the patient to the event of MDR-TB.

2. **Extensively-Drug Resistant Tuberculosis (XDR-TB):**

In March 2005, the middle for disease control and prevention (CDC) first introduced the term drug resistant TB (XDR-TB). XDR-TB could also be defined as insensitivity to fluoroquinolones such as levofloxacin and moxifloxacin, and any of the 2nd line injectable drugs amikacin, kanamycin and also capreomycin additionally to resistance to the first line drugs isoniazid and rifampicin. Extensively drug resistant TB occurs as a consequence of mishandling the MDR-TB patient. By the top of the year 2012, 92 countries reported with XDR-TB cases. XDR-TB contains highly resistant strains that are even more complicated to treat than that of MDR-TB. The management of XDR-TB requires better resources and increased financial support. It engages in higher transmission of the resistant strain especially in low income community. Mismanagement during the treatment results in higher increase within the appearance of resistant strains transmitted from one person to a different. Success rate of XDR-TB treatment is less than those of MDR-TB. Early identification of the resistance and diagnosis, careful treatment of the MDR-TB patient can help prevent XDR-TB cases. XDR-TB treatment duration include a minimum of 18–24 months approximately, and therefore the agents include those of the firstly used drugs and use of the 2nd line drugs accurately with proper maintenance. Treatment success can be highly accomplished in XDR-TB by the utilization of probably 6 drugs in the early stages of therapy followed continually by four drugs. Linezolidis costly but it's known to be useful in XDR-TB management. Thioridazine and clofazimine also are anti TB drugs which will also play a role in XDR-TB treatment.

3. **Total-Drug Resistant Tuberculosis (TDR-TB):**

Mycobacterium tuberculosis strain that possesses resistance to all or any first line drugs (Isoniazid, rifampicin, streptomyces, pyrazinamide, ethambutol) and second line drugs (Ethionamide, para-amino 2-hydroxybenzoic acid, cycloserine, ofloxacin, amikacin, ciprofloxacin, capreomycin and kanamycin) are mentioned as totally drug resistant. TDR-TB isolates show certain variation morphologically when determined at the cellular and molecular level. Employing transmission microscope displays, varying structures are namely round, oval and multiple branching forms. It possesses cell membrane that's thicker than the MDR-TB isolates, budding formation, symmetrical and asymmetrical. Till date there's no drug available to cure TDR-TB. Only careful management of MDR-TB and XDR-TB patients is that the present option.

DRUGS USED IN THE TREATMENT OF TB:

(A) FIRST LINE DRUGS:

1. **ISONIAZID:**

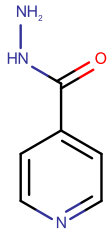


Fig.1 Isoniazid

Figure 1 Isoniazid (INH) is a pro-drug activated in *M. tuberculosis* cytoplasm by the enzyme Kat-G, a catalase-peroxidase encoded by the kat-G gene. Once activated, the drug inhibits the synthesis of mycolic acids forming the cell membrane by inactivation of the enzyme InhA. The most mechanisms of resistance to isoniazid include (i) the alteration of KatG function, preventing the activation of the pro-drug, or (ii) the increased expression of InhA. The well characterized KatG Ser315 and fabG1 −15C mutations were observed in 64% and 19% of isolates, respectively, with an isoniazid-resistant (INH-R) phenotype in line with a meta-analysis of over 11 000 isolates. The catalase-peroxidase also plays a crucial role in M. tuberculosis fitness by protecting the bacterium from host-mediated oxidative stress. However, Kat-G Ser315Thr mutants show no impaired virulence during infections and keep its full catalase-peroxidase activity.

2. **ETHAMBUTOL:**

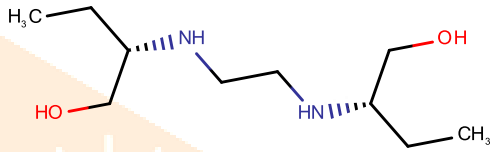


Fig.2 Ethambutol

Figure 2 Ethambutol drugs inhibit arabinosyl transferase and disrupt the biosynthesis of arabino-galactam within the cytomembrane. Resistance to Ethambutol is caused by mutation of the emb gene by altering its protein structure or by over expressing itself, overcoming the antimicrobial activity level of Ethambutol which ends in loss of its efficiency. Mutation within the gene emb-B at the position 306 replaced a single methionine with leucine or isoleucine frequently leads to ethambutol resistance. Another enzyme that takes part within the cell membrane synthesis known because the decaprenyl-phosphate 5-phosphoribosyltransferase (DPPR synthase) encoded by the gene ubiA and mutation during this gene led to higher level of resistance to ethambutol together with the emb-B mutation.

3. **PYRAZINAMIDE:**

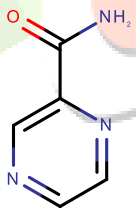


Fig.3 Pyrazinamide

Figure 3 Pyrazinamide is merely utilized in combination with other drugs like isoniazid and rifampicin within the treatment of tubercle bacillus and as directly observed therapy (DOT). It's never used on its own. It's no other indicated medical uses. especially, it's not wont to treat other mycobacterium; Mycobacterium bovis and leprosy bacillus are innately immune to pyrazinamide. Pyrazinamide is employed within the first 2 months of treatment to scale back the duration of treatment required. Regimens not containing pyrazinamide must be taken for 9 months or more.

Pyrazinoic acid was thought to inhibit the enzyme carboxylic acid synthase (FAS) I, which is required by the bacterium to synthesize fatty acids [18] although this has been discounted. The buildup of pyrazinoic acid was also suggested to disrupt membrane potential and interfere with energy production, necessary for survival of M. tuberculosis at an acidic site of infection. However, since an acidic environment isn't essential for pyrazinamide susceptibility and pyrazinamide treatment doesn't cause intra-bacterial acidification or rapid disruption of membrane potential, this model has also been discounted. Pyrazinoic acid was proposed to bind to the ribosomal protein S1 (RpsA) and inhibit trans-translation, but more detailed experiments have shown that it doesn't have this activity.

4. STREPTOMYCIN:

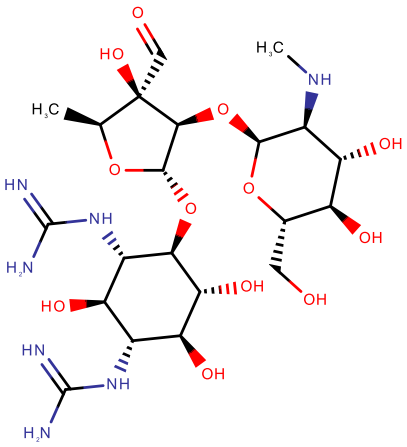


Fig. 4 Streptomycin

Figure 4 Streptomycin is an aminoglycoside which is active against the growing bacilli. This drug acts as an inhibitory agent of protein biosynthesis and intervenes within the initiation of translation and capacity of ribosomal proofreading. The structure of 16S rRNA is stabilized by S12 ribosomal protein, however base mutation within the rpsL gene causes resistance to streptomycin leading to the destabilization of the 16S rRNA.

5. RIFAMPICIN:

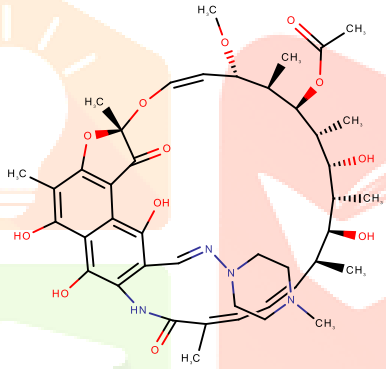


Fig. 5 Rifampicin

Figure 5 Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA rifampicin binds to the pocket of the RNA polymerase β subunit within the DNA/RNA channel, but far away from the active site. The inhibitor prevents RNA synthesis by physically blocking elongation, and thus preventing synthesis of host bacterial proteins. By this "steric-occlusion" mechanism, rifampicin blocks synthesis of the second or third phosphodiester bond between the nucleotides within the RNA backbone, preventing elongation of the 5' end of the RNA transcript past over 2 or 3 nucleotides.

(B) SEDOND LINE DRUG:

1. FLUROQUINOLONE:

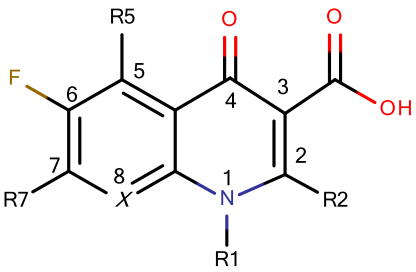


Fig. 6 General Structure of Fluoroquinolone

Table: 1 Derivatives of Fluoroquinolone

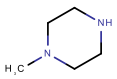
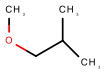
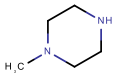
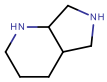
Sr. No.	Name of Compound	X	R1	R5	R7
1.	Nalidixic Acid	N	C_2H_5	H	CH_3
2.	Pefloxacin	C	C_2H_5	H	
3.	Ciprofloxacin	C		H	
4.	Levofloxacin	C		H	
5.	Moxifloxacin	C-OMe		H	
6.	Sitafloxacin	C-Cl		H	

Figure 6 Fluoroquinolones are a category of antibiotics approved to treat or prevent certain bacterial infections. The fluoroquinolone antibiotics include ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), and ofloxacin (Floxin). Fluoroquinolones kill tubercle bacillus , the causative agent of tuberculosis, by increasing levels of DNA breaks generated by gyrase, an important type II topoisomerase that regulates DNA topology thereby enabling these agents to be both specific and bactericidal.

2. KANAMICIN:

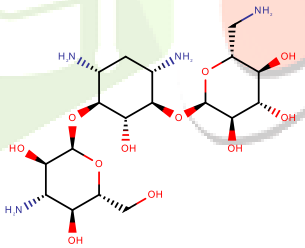


Fig. 7 Kanamycin

Figure 7 These four drugs are utilized in the medication and management of MDR-TB. Kanamycin and Amikacin altered the 16S rRNA level by interfering with the protein synthesis. Mutation within the gene is encoding the 16S rRNA end in higher increasing state of resistance to kanamycin and amikacin. Mutation at the -10 and -35 position within the cis-promoter region encoding the aminoglycoside acetyltransferase induces low level kanamycin resistance. In various studies cross resistance to Capreomycin and viomycin was observed. The rRNA methyl-transferase encoded by the tyl-A gene is liable for 2-O-methylation of the ribose in rRNA. Mutation within the tyl-A gene causes resistance to capreomycin and viomycin. Mutation in 23S rRNA of the gene also is leads to capreomycin and viomycin resistance.

3. ETHIONAMIDE:

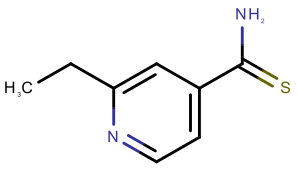


Fig. 8 Ethionamide

Figure 8 Ethionamide may be a nicotinamide derivative, with antibacterial activity, wont to treat tuberculosis. Although the precise mechanism of action of ethionamide is unknown, it's going to inhibit the synthesis of mycolic acid, a saturated carboxylic acid found within the bacterial cell membrane, thereby inhibiting bacterial cell membrane synthesis. . It

acts with the assistance of the enzyme mono-oxygenase that activates it. It inhibits the NADH dependent ACP reductase enzyme by interfering with the mycolic acid biosynthesis that forms adducts with NAD. Mono-oxygenase is coded by the gene ethA, ethR and inhA,mutation in these genes results in ethionamide resistance. The gene InhA is targeted by both isoniazid and ethionamide then resistance to one drug results in the resistance to a different.

4. **PARA AMINO SALICYLIC ACID:**

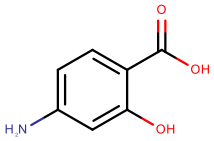


Fig. 9 Para Amino Salicylic Acid

Figure 9 This drug is an analog to amino carboxylic acid and interferes with the folate synthesis process. The enzyme dihydrofolate synthase encoded by folC gene activates the para amino 2-hydroxybenzoic acid. Missense mutation during this gene causes resistance to para amino 2-hydroxybenzoic acid. The activated anti-metabolite (PAS) interferes with the activity of the enzyme encoded by dfrA and mutation during this gene also induces resistance to PAS.

5. **CYCLOSERINE:**

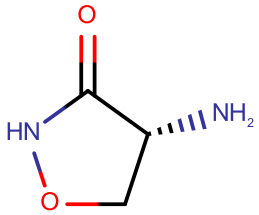


Fig. 10 Cycloserine

Figure 10 Cycloserine disrupts D-alanine incorporation into peptidoglycan during bacterial cell membrane synthesis. As a cyclic analogue of D-alanine, cycloserine acts against two crucial enzymes important within the cytosolic stages of peptidoglycan synthesis: alanine racemase (Alr) and D-alanine ligase (Ddl).

6. **MACROLIDES:**

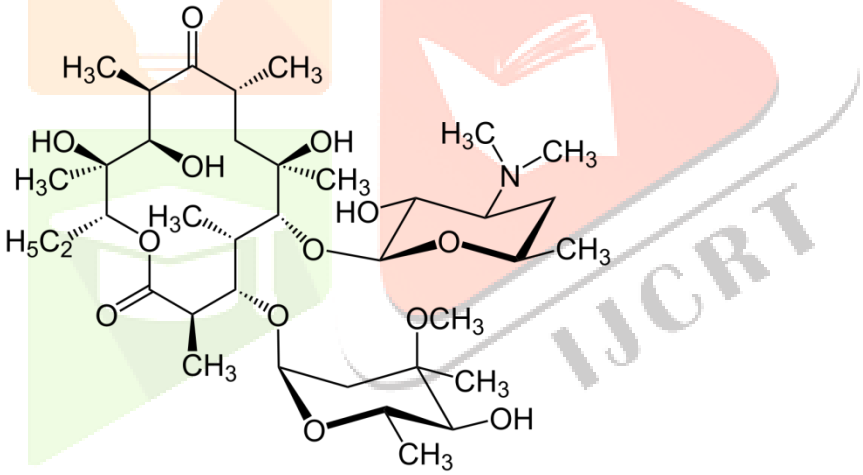


Fig. 11 Macrolide antibiotics

Figure 11 Macrolide antibiotics do so by binding reversibly to the P site on the 50S subunit of the bacterial ribosome. This action is taken into account to be bacteriostatic. Macrolides are actively concentrated within leukocytes, and thus are transported into the location of infection. The drug's activity is blocked by the expression of the gene emr37.

7. **LINEZOLID:**

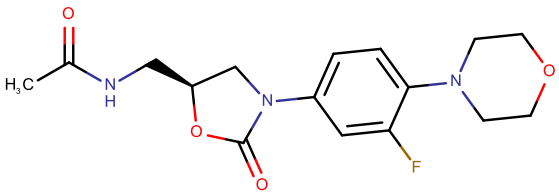
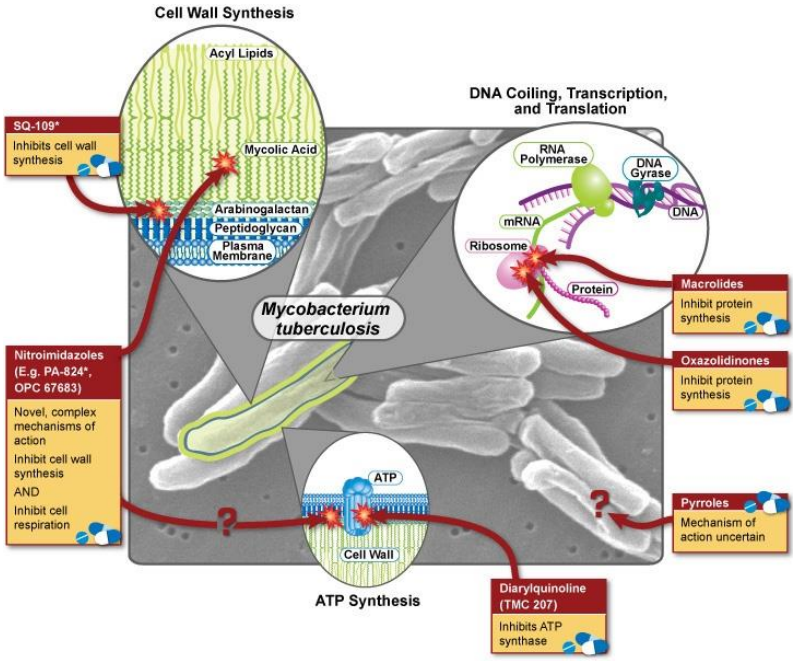


Fig. 12 Linezolid

Figure 12 Linezolid disrupts bacterial growth by inhibiting the initiation process of protein synthesis. A mechanism of action that's unique to the present class of medicine. It's well absorbed with high bioavailability that permits conversion to oral therapy as soon because the patient is clinically stable.



DIAGNOSIS OF TB:

(A) Microscopy and culture for the diagnosis of TB in children:

Smear microscopy is an insensitive test for TB in children. A recent meta-analysis of 15paediatric studies which compared standard microbiological testing to nucleic acid amplification testing with X-pert MTB/RIF, found the pooled sensitivity of smear microscopy to be 22% (gastric aspirate) or 29% (induced/expectorated sputum) compared with mycobacterial culture. Mycobacterial culture remains the foremost sensitive method for microbiological confirmation of TB in children, but since many children are diagnosed clinically with PTB, despite negative microbiological testing, culture is taken into account to be an imperfect reference standard. For instance, within the same meta-analysis, the yield of mycobacterial culture amongst 939 children with a diagnosis of TB was only 24.4%. The apparent low yield of culture may reflect the insensitivity of culture, the poor specificity of clinical diagnosis, or presumably the mixture of both. It is perhaps insufficiently recognized that mycobacterial culture isn't uniformly well implemented. Although automated liquid culture systems are now widely used, and significantly more sensitive than culture on solid media, the method of preparing a sample for culture is technically demanding. Potentially contaminated samples, like sputum, undergo decontamination to get rid of rapidly growing bacteria, typically with sodium hydroxide, before culture. The concentration of caustic soda used varies by laboratory. Whilst this has not been well-studied, it's possible that less heavily contaminated samples from children may require less harsh decontamination protocols than those from adults, and that this might affect mycobacterial yield. In one before-and-after study, the change from1.5% to a quarter caustic soda concentration was related to a rise in *M. tuberculosis* yield from 6.0 to 9.7% with no corresponding increase in contamination rate. The optimization of mycobacterial culture methods for pediatric samples, and for different respiratory sample types, requires further study.

(B) Nucleic acid amplification tests for the diagnosis of TB in children:

The development and implementation of automated macromolecule amplification tests (NAATs) for TB has been a big advance. X-pert MTB/RIF has led the sector; however the BD MAX MDR-TB assay (20) from Becton Dickinson, has recently demonstrated similar accuracy to X-pert MTB/RIF in clinical testing. There are several important advantages to those tests: both are simultaneously ready to detect the presence of M. tuberculosis DNA and identify resistance to rifampicin (the BD MAX assay also identifies most cases with isoniazid resistance), tests are rapid, operator dependence is greatly reduced compared to earlier NAATs, and therefore the X-pert MTB/RIF platform is comparatively small, and suitable for testing at decentralized sites, closer to the point-of-care. A meta-analysis of the accuracy of one X-pert MTB/RIF test in children found a pooled sensitivity of 62% and 66% for sputum and gastric aspirate respectively, compared with a microbiological reference standard. Specificity for both sample types was 98%. The test identified the presence of M. tuberculosis DNA in just 2% of clinically diagnosed (but culture-negative) cases. Testing a further sample with Xpert MTB/RIF increased the diagnostic yield (over one Xpert MTB/RIF test) by between 8 and 20%. A newer version of the Xpert MTB/RIF assay, Xpert MTB/RIF Ultra (Ultra) has improved sensitivity (with slightly reduced specificity) in adults. Ultra, done on induced or expectorated sputum or bronchoalveolar lavage fluid, has recently been evaluated in several pediatric cohorts where it showed improvement in sensitivity over Xpert MTB/RIF of between 2% and 10%, with marginally lower specificity. The diagnosis of tuberculosis is often initiated by investigating the medical record of the patient. Before giving any preventive treatment, patients with active TB should be screened for symptoms. Examination of the fitness of the patient is to be followed by test for infection by the bacterium. Resistance to drug also can be tested by isolating the tubercle bacilli and performing the drug susceptibility testing (DST). Diagnosis of drug resistant TB is additionally done by whole genome sequencing and for identifying the mutations within the genome of the M. tuberculosis. Even complete drug resistant mutations in MTB are often understood by whole genome sequencing method resulting in a more appropriate therapy. a replacement study also shows that isoniazid, ethambutol, rifampicin, streptomycin, ofloxacin and amikacin resistance might be predicted by WGS within the future during a faster and economical way. New techniques are developed including the utilization of assay like radiological screening. Detection of tuberculosis through computer aided digital chest X-rays is out there. The test for M. tuberculosis also can be done through skin test which is additionally referred to as Mantoux tuberculin skin test, the diagnostic test is usually done by injecting within the under arm on the lower spare tuberculin fluid. The positive TB or negative TB is typically checked by diameter of ask in reaction

measured in millimeters. Urinary LAM test can also be used for diagnosis of tuberculosis. Mortality reduction of tuberculosis has resulted with the utilization of LAM test because it provides efficient result about patients co-infected with HIV. the idea of LAM test was promoted by the production of Lipo-arabino mannam (LAM) by the bacteria once they replicate inside the host. Molecular tastings which are considered as the foremost advanced techniques are often used for diagnosis of tuberculosis by detecting the mutations or the genetic material of the tubercle bacillus. Molecular test are often done by Xpert MTB/RIF, Real time MTB and Fluoro Type MTBDR. Drug susceptibility testing is often used for the diagnosis of tuberculosis strain by culturing with the drug. If the bacterium strain shows resistance to the firstly used drug rifampicin and isoniazid then they're diagnosed as multidrug resistant TB. After confirmation of resistance within the firstly used drug, 2nd line drug susceptibility test is completed. If there's an appearance of resistance to 2nd line drugs including fluoroquinolones then the patient is diagnosed with extensively drug resistance TB. For rapid diagnosis of resistance posed by tuberculosis, nuclei assay are also available.

TUBERCULOSIS PREVENTIVE TREATMENT:

Globally, implementation of TPT remains sub-optimal, particularly in many low- and middle-income countries where TB remains a significant public ill health. Barriers to TPT scale-up include insufficient awareness of the importance of TPT by healthcare workers, limited engagement of TB control programmes in preventive strategies, a limited capacity to diagnose LTBI and excluding TB disease, also as insufficient availability and duration of treatment options. New advances promise to beat many of those limitations. Importantly, shorter and more acceptable TPT regimens using less toxic drugs have recently been recommended by WHO (World Health Organization, 2020a, World Health Organization, 2020b). However, for these shorter duration TPT regimens to substantially alter the present TB epidemic trajectory, robust operational research is required to guide its implementation in several settings. National TB programmes are encouraged to develop tailored strategies to screen and treat high-risk populations like close contacts (World Health Organization, 2018). The growing number of therapeutic options available to patients also enables a more patient-centred approach to TPT. The supply of multiple effective treatments for LTBI offers patient greater choice (World Health Organization, 2018). Digital patient decision aids, Smartphone Apps and online risk calculators can provide individual risk-benefit estimates, explore personal priorities, and consider individual risks of toxicity. Samples of decision aids include tstin3d.com and PERISKOPE-TB (Gupta, Calderwood et al. 2020). However, further research is required to guide the adoption of digital tools during a range of settings. A health system approach can help programmes to spot the structural changes required to deliver TPT at scale. The six elements of the WHO Health Systems framework include service delivery, health workforce, health information systems, access to preventive treatment, financing and leadership/governance (World Health Organization, 2010). Developing an area plan that addresses each of those elements, amid adequate investment, will help to make sure TPT programs are sustainable. Transmission of drug resistance are often prevented by undertaking community awareness about TB, hygiene, pollution free environment and any symptoms associated with the disease must immediately be reported to doctor, and early identification and diagnosis would offer an honest success rate. quite 50 for cover from TB infection was found to be supported by M72/AS01 (Glaxo Smith Kline, London UK) a completely unique vaccine in 2018 phase 2b study . Health finance for the control of TB worldwide would play a really important role, as low economic nations are primarily susceptible to this disease. Laboratory workers are more susceptible to infection than the overall community with their day to day handling the pathogenic or non-pathogenic bacteria, as such, additional prevention measures must be taken for them. Direct contact with MDR-TB/XDR-TB patient must be restricted so as to scale back the danger of transmission. Any immune compromised individual if met with MDR/XDR-TB patient must be quickly diagnosed and if required should be treated with any two of the anti-TB drugs.

CONCLUSION:

M. Tb resistance is attributed to the spontaneous mutation to the targeted protein that interfere the binding site of used drugs. Drug resistant TB is the condition when tuberculosis infection does not respond or resistant to one or more of anti-mycobacterial drugs. Resistance may develop due to so many factors such as failure to follow TB regimen or inadequate TB treatment or improper diagnosis. However, owing to the advent of drug-resistant TB strains, new drugs are immediately required and thus efforts have been twisted towards natural sources to finding of new TB leads. The bioactive moiety from natural origin and their derivatives have been described to display significant inhibition of the causative agent and few of them have been selected as lead molecules for the development of new mechanisms based antitubercular drugs.

REFERENCES:

1) L. K. Dahiwade, S. P. Rochlani, Dr. P. B. Choudhari, Mr. R. P. Dhavale and Dr. H. N. More, Development of 'S', 'N' Heterocycles as Antimycobacterials Targeting Fatty Acid Biosynthesis, *Current Computer-Aided Drug Design*, 2019, Vol. 15, No. 3
2) Pramod S. Phatak, Rajubai D. Bakale, Sambhaji T. Dhumal, Lalita K. Dahiwade, Prafulla B. Choudhari, Synthesis, antitubercular evaluation and molecular docking studies of phthalimide bearing 1, 2, 3-triazoles, *Synthetic communications*, 2019, 49:16
3) C.A. Whittle, C.G. Extavour, Expression-linked patterns of codon usage, amino acid frequency, and protein length in the basally branching Arthropod Parasteatoda tepidariorum, Genome Biol. Evol. 8 (9) (2016) 2722–2736.
4) S.K. Sharma, A. Mohan, Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control, Chest 130 (1) (2006) 261–272.
5) J. Furin, H. Cox, M. Pai, Tuberculosis, Lancet 393 (10181) (2019) 1642–1656.
6) W.H. Organization, World Health Organization Multidrug and Extensively Drug resistant TB (M/XDR-TB): 2010 Global Report on Surveillance Andresponse, World Health Organization, Geneva, Switzerland, 2010.
7) E. Harding, WHO global progress report on tuberculosis elimination, Lancet *Respir. Med.* 8 (1) (2020) 19.
8) Y. Zhang, W. Yew, Mechanisms of drug resistance in Mycobacterium tuberculosis: update 2015, Int. J. Tuberc. Lung Dis. 19 (11) (2015) 1276–1289.
9) J.G. Pasipanodya, T. Gumbo, A new evolutionary and pharmacokinetic–pharmacodynamic scenario for rapid emergence of resistance to single and multiple anti-tuberculosis drugs, Curr. Opin. Pharmacol. 11 (5) (2011) 457–463.

10) L. Nguyen, Antibiotic resistance mechanisms in M. tuberculosis: an update, Arch. Toxicol. 90 (7) (2016) 1585–1604.
11) Y. Zhang, Persisters, persistent infections and the Yin–Yang model, Emerg. Microbes Infect. 3 (1) (2014) 1–10.
12) P. Gurumurthy, G. Ramachandran, A.H. Kumar, S. Rajasekaran, C. Padmapriyadarsini, S. Swaminathan, P. Venkatesan, L. Sekar, S. Kumar, O. Krishnarajasekhar, Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis, Clin. Infect. Dis. 38 (2) (2004) 280–283.
13) H.E. Takiff, The Molecular Mechanisms of Drug Resistance in Mycobacterium tuberculosis, Multidrug-resistant Tuberculosis, Springer, 2000, pp. 77–114
    A. Koch, H. Cox, V. Mizrahi, Drug-resistant tuberculosis: challenges and opportunities for diagnosis and treatment, Curr. Opin. Pharmacol. 42 (2018) 7–15.
14) B.G. Spratt, Resistance to antibiotics mediated by target alterations, Science 264 (5157) (1994) 388–393
    A. A. Agyeman, R. Ofori-Asenso, Tuberculosis—an overview, J. Public Health Emerg. 1 (2017), 7-7
15) J. Armstrong, P.A. Hart, Phagosome-lysosome interactions in cultured macrophages infected with virulent tubercle bacilli. Reversal of the usual nonfusion pattern and observations on bacterial survival, J. Exp. Med. 142 (1) (1975) 1–16
16) Z.A. Malik, G.M. Denning, D.J. Kusner, Inhibition of Ca2+ signaling by Mycobacterium tuberculosis is associated with reduced phagosome–lysosome fusion and increased survival within human macrophages, J. Exp. Med. 191 (2) (2000) 287–302.
17) N.W. Schluger, The pathogenesis of tuberculosis: the first one hundred (and twenty-three) years, Am. J. Respir. Cell Mol. Biol. 32 (4) (2005) 251–256.
18) A.M. Dannenberg Jr., G.A. Rook, Pathogenesis of pulmonary tuberculosis: an interplay of tissue-damaging and macrophage-activating immune responses—dual mechanisms that control bacillary multiplication, Tuberculosis, Am. Soc. Microbiol. (1994) 459–483.
19) D. Falzon, H.J. Schünemann, E. Harausz, L. Gonzalez-Angulo, C. Lienhardt, E. Jaramillo, K. Weyer, World Health Organization treatment guidelines for drug resistant tuberculosis, 2016 update, Eur. Respir. J. 49 (3) (2017).
20) Jafari E, Khajouei MR, Hassanzadeh F, Hakimelahi GH, Khodarahmi GA. Quinazolinone and quinazoline derivatives: recent structures with potent antimicrobial and cytotoxic activities. Res. Pharm. Sci. 2016;11:1–14.
21) Tiwary BK, Pradhan K, Nanda AK, Chakraborty R. Implication of quinazoline-4 (3H)-ones in medicinal chemistry: a Brief review. J. Chem. Biol. Ther. 2015; 1. 2572-0406.
22) Griess P. The first report of 4(3H)-quinazolinone compound. J Prakt Chem 1869: 369–71.
23) Sharma SD, Kaur V. Synthesis of 3-Oxa- and 3-Aza-1-dethiacepham analogs. Synthesis 1989:677–80.
24) Moore JA, Sutherland GJ, Sowerby R, Kelly EG, Palermo S, Webster W. Reactions of anthranilamide and o-aminoacetophenone with benzil and benzoin. J Org Chem 1969;34:887–92.
25) Cai GP, Xu XL, Li ZF, Weber WP, Lu P. A one-pot synthesis of 2-aryl-2, 3-dihydro-4 (1H)-quinazolinones by use of samarium iodide. J Heterocycl Chem 2002;39: 1271–2.
26) Asakawa H, Matano M. Synthesis of 6-Chloro-5-sulfamoyl-and 6-Chloro-3-sulfamoylanthranilic acid derivatives. Chem Pharm Bull 1979;27:1287–98.
27) Connolly DJ, Cusack D, O'sullivan TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. Tetrahedron 2005;61:10153–202.
28) Su WK, Yang BB. Reductive cyclization of nitro and azide compounds with aldehydes and ketones promoted by metallic samarium and catalytic amount of iodine. Aust J Chem 2002; 55:695–7.
29) Wang J, Zha S, Chen K, Zhang F, Song C, Zhu J. Quinazoline synthesis via Rh (III)-catalyzed intermolecular C-H functionalization of benzimidates with dioxazolones. Org Lett 2016; 18:2062–5.
30) Shi DQ, Rong LC, Wang JX, Wang XS, Tu SJ, Hu HW. Synthesis of 1, 2-dihydro quinazolin-4 (3H)-ones promoted by low-valent titanium. Chem J Chin Univ 2004; 25:2051–3.
31) Bahadorikhalili S, Mahdavi M, Ma'mani L, Shafiee A, Mahdavi H, Akbarzadeh T. Palladium functionalized phosphinite polyethyleneimine grafted magnetic silica nanoparticles as an efficient catalyst for the synthesis of isoquinolino [1,2-b] quinazolin-8-ones. New J Chem 2018;42:5499–507.
32) Shi DQ, Rong LC, Wang JX, Zhuang QY, Wang XS, Hu HW. Synthesis of quinazolin- 4(3H)-ones and 1,2-dihydroquinazolin-4(3H)-ones with the aid of a low-valent titanium reagent. Tetrahedron Lett 2003;44:3199–201.
33) Shi DQ, Shi CL, Wang JX, Rong LC, Zhuang QY, Wang XS. An efficient synthesis of quinazoline derivatives with the aid of low-valent titanium reagent. J Heterocycl Chem 2005; 40:173–83.
34) Dabiri M, Salehi P, Otokesh S, Baghbanzadeh M, Kozehgarya G, Mohammadi AA. Efficient synthesis of mono-and disubstituted 2,3-dihydroquinazolin-4(1H)-ones using KAl (SO4)2·12H2O as a reusable catalyst in water and ethanol. Tetrahedron Lett 2005; 46:6123–6.
35) Salehi P, Dabiri M, Zolfigol MA, Baghbanzadeh M. A novel method for the one-pot three-component synthesis of 2,3-dihydroquinazolin-4(1H)-ones. Synlett 2005; 7: 1155–7.
36) Baghbanzadeh M, Salehi P, Dabiri M, Kozehgarya G. Water-accelerated synthesis of novel bis-2, 3-dihydroquinazolin-4 (1H)-one derivatives. Synthesis 2006; 2:344–8.
37) Dutta A, Damarla K, Bordoloi A, Kumar A, Sarma D. KOH/DMSO: a basic suspension for transition metal-free Tandem synthesis of 2,3-dihydroquinazolin-4 (1H)-ones. Tetrahedron Lett 2019; 60:1614–9.
38) Dutta A, Damarla K, Kumar A, Saikia PJ, Sarma D. Gemini basic ionic liquid as bifunctional catalyst for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones at room temperature. Tetrahedron Lett 2020; 61:151587. Niementowski S. Synthesen von chinazolinverbindungen. J Prakt Chem 1895