

Drug resistance in Mycobacterium Tuberculosis

Challenges for low and middle income countries in achieving global eradication

ABSTRACT

The COVID-19 pandemic has also had a significant impact on the detection and management of infectious diseases worldwide. As the healthcare resources struggle to deal with the pandemic, there is widespread fear that there will be a rise in other infections and non-communicable diseases. Mycobacterium Tuberculosis remains one of the highest cause of mortality and morbidity in the world with 10 million new cases, 1.4 million deaths and nearly half a million cases of drug resistant TB, in 2019.

The need of the hour is to prevent the rise of drug resistance in TB. The rise in drug resistance can be mainly attributed to failure to adhere to treatment regimens. Recent studies show that the exposure of bacteria to sublethal levels of bacterial antibiotics, promotes cellular mutations, leading to increased mutations promoting drug resistance. Because of the problems associated with detection and treatment of drug resistant tuberculosis, it is of paramount importance that we aim to implement stringent measures of primary and secondary prevention against cases of drug sensitive tuberculosis to prevent the rise of drug resistance. It is important to highlight the importance of DOTS while talking about measures of primary and secondary prevention. The involvement of the multidisciplinary health team and auxiliary health workers to monitor the treatment of affected patients cannot be stressed upon enough, since this is the most simple and effective way to prevent treatment failure.

Furthermore, the cost of treatment of MDR-TB remains out of reach of the middle and lower middle income strata of society. It is the need of the hour to lower the cost of drugs as well as provide easy and affordable access to rapid investigations to detect drug resistance

Keywords

Mycobacterium Tuberculosis; Drug resistant TB; Directly observed therapy;

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Introduction

Tuberculosis (TB) is an infectious disease caused by the infectious agent *Mycobacterium Tuberculosis* (MTB) bacteria. It primarily affects the respiratory system; however, it can affect other organs and organ systems such as the gastrointestinal system, the central nervous system and the musculoskeletal system. The primary symptoms of TB are chronic cough with expectoration, haemoptysis, fever, night sweats and weight loss. Other symptoms will depend on the organ system affected. The route of spread is airborne, and via droplet spread.^[1]

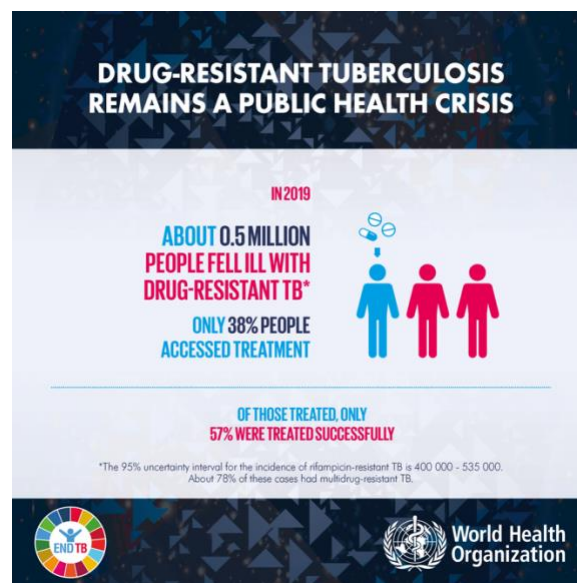
TB places a major burden on health worldwide with 10 million people contracting the infection and 1.4 million people succumbing to death such as in 2019 alone. TB has been the leading cause of death from an infectious agent ahead of Human Immunodeficiency viral infection- Acquired immunodeficiency syndrome (HIV/AIDS).^[2]

Tuberculosis is a curable disease. The current standard regimen for the treatment of TB recommends an

intensive phase of medication for 2 months, followed by a continuation phase for 4-7 months. The main drugs used in the treatment are Isoniazid, Rifampicin, Ethambutol, Pyrazinamide and Streptomycin. Further, effective treatment strategies have been implemented by governments worldwide, in the form of DOTS (Directly Observed Treatment, Short course), which has proven to break the chain of infection and reduce re-infection rates.^[3]

Drug resistance in Tuberculosis

A major barrier in the eradication of TB is drug resistance. Worryingly, the emergence of Multidrug Resistant Tuberculosis (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB) have made it difficult to effectively treat and break the chain of transmission. Multidrug-Resistant Tuberculosis (MDR-TB) is a strain that does not respond to Isoniazid and Rifampicin. Extensively Drug-Resistant TB (XDR TB) is a rare variation of Multidrug-Resistant Tuberculosis (MDR TB) that is resistant to isoniazid and rifampicin, along with any one of the fluoroquinolones and at least one of three injectable second-line drugs.



Mechanisms of drug resistance

There are numerous mechanisms that contribute to drug resistance. These can be grouped into natural mechanisms, and those acquired through genetic mutations.

Natural mechanisms

Natural mechanisms include factors involving the cell wall of *Mycobacterium Tuberculosis*. Although *Mycobacterium* is classified as being gram positive,

their cell wall has a unique structure which gives it properties similar to those of gram-negative bacteria. The cell wall is composed of peptidoglycan sacculus, which are covered by an arabinogalactan layer. This makes it hydrophilic and thereby prevents the transport of hydrophobic molecules. Further, this layer is covalently linked to a chain of mycolic acids and long chain fatty acid that stop the transfer of both hydrophobic and hydrophilic molecules across. This makes drug delivery a difficult process.^[4]

Another natural mechanism that Mycobacterium Tuberculosis demonstrates is that of efflux pumps. Efflux pumps have been noted in the use of *Bedaquiline*, the first new anti-TB drug to be approved by the FDA in over 40 years to treat Multidrug Resistant Tuberculosis. However, recent studies have suggested that *Bedaquiline* resistance was noted in MDR TB, via efflux pumps that actively pump the drug molecules out of the cell. Efflux pumps also played a large part in resistance against Clofazimine via cross reactivity. An attempt has been made to use efflux pump inhibitors to aid treatment in MDR-TB, since this reduces resistance to an extent. An example of efflux pump inhibitors is Verapamil, a calcium channel blocker. It works by causing a decrease in transmembrane potential which reduces the activity of efflux pumps. This helps to reduce the minimum inhibitory concentration of *Bedaquiline*, thereby restoring its efficacy. ^[5]

Genetic mutation

An example of genetic mutation resulting in drug resistance can be noted in the case of Pyrazinamide. Pyrazinamide is a pro-drug, which is converted within the Mycobacterium Tuberculosis to its active form pyrazinoic acid and this disrupts membrane transport across the cell wall. The conversion into the active form is facilitated by an enzyme called pyrazinamidase/ nicotinamidase encoded by the *pncA* gene. Varied expression of the *pncA* gene can determine whether the bacteria is susceptible or resistant to Pyrazinamide. Decreased expression of the *pncA* gene leads to increased resistance against Pyrazinamide, one of the primary drugs used to treat TB. ^{[6] [7]}

Another example of drug resistance achieved through genetic mutation can be seen in resistance displayed against Rifampicin. Rifampicin works by binding to the beta subunit of RNA Polymerase, thereby disrupting RNA transcription. The beta subunit of RNA Polymerase, is coded for by the *rpoB* gene. Genetic mutations in this gene alter the sequence of amino acids of the beta subunit and thereby disrupt the binding of rifampicin with RNA polymerase. ^[8]

Clinical impact

According to drug resistance surveillance data, as many as 240,000 people died from MDR-TB in 2016. Further, the number of XDR-TB cases was as high as 8000, with 123 countries reporting at least 1 XDR-TB case. ^[9]

Even though a national program for the treatment and prevention of Tuberculosis (RNTCP) has existed since

1997, India alone registered an estimated 130,000 drug resistant TB cases in 2018. Further, only an estimated 44% of drug resistant cases were diagnosed and only 35.8% received treatment. The treatment of MDR-TB in India started as early as 2007, however the country continues to register a worryingly high number of drug resistant Tuberculosis cases. ^[10]

The COVID-19 pandemic has also had a significant impact on the detection and management of infectious diseases worldwide. As the healthcare resources struggle to deal with the pandemic, there is widespread fear that there will be a rise in other infections and non-communicable diseases.

The need of the hour is to prevent the rise of drug resistance. The rise in drug resistance can be mainly attributed to failure to adhere to treatment regimens. Recent studies show that the exposure of bacteria to sublethal levels of bacterial antibiotics, promotes cellular mutations, leading to increased mutations promoting drug resistance. ^[11]

Detecting Drug Resistant MTB

There are a number of investigations which are commonly employed in the detection of MDR-TB and XDR-TB. One of the most common methods to test for drug resistance is via solid culture methods. Using the Lowenstein-Jensen (LJ Media), Drug Sensitivity testing (DST) can be carried out, and MDR TB can be identified through minimum inhibitory concentrations (MIC) of antitubercular drugs.

An alternative which is being used increasingly to detect MDR-TB, is that of liquid culture media, which is more sensitive than solid media. Examples of these include BACTEC 460®, and the more widely used, Mycobacteria Growth Indicator Tube system (MGIT®). Along with these, newer phenotypic and molecular methods have been developed in order to identify MDR-TB. An example of newer phenotypic methods is TK Media®. TK media® displays colour changes in the presence of MTB even before the physical appearance of mycobacterial growth, thereby allowing for rapid detection. ^[12]

However, despite the abundance of tests available to us to detect MTB and drug resistance, there are two major factors- *time and affordability*, which hinder the large scale application of these investigations. The results of drug sensitivity testing take 3-8 weeks for solid media, and around 1-3 weeks for liquid media. ^[13] Although these tests are relatively cost-effective, and do not require sophisticated equipment, such delays can result in inadequate or ineffective treatment, which not only leads to increased amount of transmission, but can yield adverse consequences for

individuals who are at increased risk of mortality, due to causes such as immunosuppression, and coinfection with HIV.

In order to minimise delays and employ increased sensitivity, the World Health Organisation (WHO) has recommended molecular methods for the detection of MTB. First recommended in 2010 for the detection of TB in adults, Xpert MTB/RIF® is a molecular test that helps to detect MTB complex and resistance to rifampicin in 2 hours using nucleic acid amplification (NAA).^[14]

However, these molecular rapid diagnosis tests present the second hindrance which is of *affordability*. In 2019, out of eight countries which recorded the highest incidence of TB patients, (India, Indonesia, Philippines, China, Pakistan, Nigeria, South Africa, Bangladesh), five out of these were classified as being low-middle/low income countries (LMIC).^[15]—An important risk factor for MTB is lower socioeconomic status, due to poor living conditions with inadequate ventilation and overcrowding. In such scenarios, it is difficult to employ tests such as Xpert MTB/RIF®, which in India have a mean cost ranging from US\$30-50^[16], a hefty price to pay for the average patient in LMICs.

Treatment of MDR-TB

The treatment of MDR-TB is usually in the form of second line anti-TB medications. However this poses a problem, since these are not as effective as first line agents, while also causing more adverse effects. Furthermore, the increased prevalence of MTB in lower socio-economic areas causes a hindrance since second line drugs are not as cost effective. For

example, in India, the current cost for treatment of drug sensitive MTB is around US\$ 50, however the cost of treatment of MDR-TB which includes drugs such as *Bedaquiline*, and other second-line antitubercular drugs amounts to around US\$3500^[17], which is almost double the amount of India's per capita income of around \$1730. While patient from more affluent strata of society tend to turn to private healthcare institutions for treatment, such options remain inaccessible for those from lower economic strata. Furthermore, even in the cases of upper and middle income strata of the society, treatment of drug resistant tuberculosis has a huge financial impact, with those from middle income strata of the society spending up to half their annual income on treatment. Although the mean treatment costs were calculated to be 480,000 Indian Rupees in 2016, the actual costs varied anywhere between 130,000 to 2,500,000 Indian Rupees.^[18]

However this is not to say that there have not been any advances made. In 2020, the WHO recommended the use of TrueNat®, a molecular diagnostic method, used to detect MTB using polymerase chain reaction (PCR), as well as resistance to rifampicin using reverse transcriptase (RT-PCR) in a period of 60-90 minutes. TrueNat® is a cost effective method now being employed in low-resource settings. It has also been incorporated Indian national TB eradication programme.^[19]

The issues of time taken for detection, as well as affordability of investigations and medications for TB, for those living in low income areas lead to the conclusion that primary and secondary care must be strengthened with the aim of prevention of progression of drug sensitive TB to drug resistant TB.



Directly Observed Therapy

One such measure that is testament to the success of primary and secondary prevention is that of DOTS and DOTS Plus programs. These are programs where nurses, auxiliary health workers, and other members of the health team work against treatment failure and non-compliance by monitoring the intake of antitubercular drugs, and monitoring adverse effects so as to prevent missed doses and create a sense of patient centred care. DOTS Plus builds upon DOTS by implementing drug resistance surveillance, DST for TB patients, and creating personalised regimens for TB patients ^[20]. Due to the above reasons, a robust system comprising of a healthcare team, consisting of healthcare workers from various domains, such as microbiologists, nurses and auxiliary health care workers, is of the essence for rapid detection, adequate treatment, monitoring of smears to prevent relapses, and drug resistance surveillance. It is of paramount importance to break the chain of transmission, and prevent resistance to as large a degree as possible.

Conclusion

Tuberculosis is an infectious disease, that due to its properties and routes of spread, is prevalent in lower socioeconomic sections of the society. Factors such as poor ventilation in households and malnutrition contribute to a favourable environment for the spread and growth of MTB. Hence it is of the essence that we focus our efforts towards such subsections of the population.

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Drug resistance in TB either through inherent mechanisms or genetic mutations has complicated an already difficult approach to fight tuberculosis. Drug resistance not only increases the cost of treatment significantly, but also might cause treatment failure due to late detection, which in certain cases can be fatal, especially in high risk patients such as those living with HIV co-infection. Treatment failures due to treatment with ineffective drugs can also lead to relapses, thereby prolonging the illness and the treatment course.

Because of the problems associated with detection and treatment of drug resistant tuberculosis, it is of paramount importance that we aim to implement stringent measures of primary and secondary prevention against cases of drug sensitive tuberculosis to prevent the rise of drug resistance.

It is important to highlight the importance of DOTS while talking about measures of primary and secondary prevention. The involvement of the multidisciplinary health team and auxiliary health workers to monitor the treatment of affected patients cannot be stressed upon enough, since this is the most simple and effective way to prevent treatment failure.

Furthermore, the cost of treatment of MDR-TB remains out of reach of the middle and lower middle class, especially in private institutions. It is the need of the hour to lower the cost of drugs as well as provide easy and low cost access to rapid investigations to detect drug resistance

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