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# WHO Short Course Regime for MDR TB – A Double Edged Sword?

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## Introduction

India has the dubious distinction of being the country with the highest quantum of multidrug-resistant (MDR) tuberculosis (TB) cases worldwide [1]. The World Health Organization (WHO) in 2016 recommended a shorter drug regimen (9–11 months) for patients with MDR TB or Rifampin(R) resistant TB who had no past history of receiving second-line drugs (SLDs) and in whom resistance to fluoroquinolones (FQ) and Second Line Injectables (SLI) has been ruled out or was considered highly unlikely [2].

A shorter regimen is a promising step towards higher MDR TB treatment success rates with reduced treatment duration ensuring good compliance as was seen the Bangladesh trial [3]. However, it also carries the risk of further enhancing drug resistance by injudicious administration to patients who are not eligible for this regime.

India is a geographically vast and diverse country. Many parts are accessible only by road or air and may be cut off at times from the country by climatic and natural factors. Cartridge-based nucleic acid amplification test (CBNAAT) is a recently introduced polymerase chain reaction (PCR) based method for detection of TB. It also detects Rifampicin resistance as it targets the rpoB gene of Mycobacterium Tuberculosis (MTB) which gives Rifampicin resistance within hours with high specificity. It

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requires very less time, human resources and calibration. Once R resistance is confirmed, the WHO short course regime is initiated and a second sample is sent for first and second Line Probe Assay (LPA). LPA results tell about Isoniazid Resistance (High/low) and resistance to FQ and SLI in addition to R-resistance.

However, the result of 2nd line LPA should be available within 7 days so that FQ and/or SLI resistance, if present, is treated by a more complex and stronger individualised regime possibly containing Bedaquiline (BDQ), a drug which has given very good results in MDR TB treatment with more extensive resistant cases. However, for LPA, much more infrastructure, expertise and human resource is required. Second line LPA is available in only larger centres at present. India is building its capacity for 2nd line LPA but this will take time and resources to develop the Infrastructure for this facility to be readily and easily accessible to many parts of the country. Due to the above mentioned difficulties, it is highly probable that many LPA reports in the far and difficult to reach states of India may not be available in 7 days and take weeks to months to be accessed.

The WHO short course regime also recommends that eligible patients would be those who have not received second line drugs in the past. This is based on the premise that resistance to 2nd line drugs is unlikely in patients who have not taken them in the past. However, there is evidence to show that a large proportion of MDR TB is not due to reactivation but due to transmission [4]. Hence absence of resistance to 2nd line drugs cannot be ruled out with a high degree of certainty simply on a past history of Non-intake.

Studies from India have shown that one third to one half of MDR TB patients may have additional FQ resistance [5,6]. One very recent study from Uttar Pradesh, the state with 20% MDR patients of India, showed that 60 % of these MDR patients were not eligible for the WHO short course regime due to primary FQ and/or SLI resistance [7].

Hence, it may be assumed that India is probably not a country where Short course MDR regime may be universally applied. It is likely that a significant proportion of patients initiated on this regime who already have resistance to FQ and/or SLI will also become resistant to other drugs in the regime due to selection pressure.

The short course MDR TB treatment uses Clofazimine as a key sterilizing drug in its entire duration, resistance to which may lead to resistance to BDQ also. BDQ shares cross resistance with clofazimine probably because of sharing common biochemistry. This has been shown by Hartkourn et al in 2014 and Almeida D in 2016 [8,9]. One third of patients with CFZ resistance may-have BDQ resistance without any exposure and all BDQ resistant patients would be resistant to CFZ [10]. Hence by a rough translation, about one-third MDR patients given short course regime may fail due to previous FQ resistance. If LPA report is not received in time, the patients who are harbouring primary FQ resistance may also become resistant to the other drugs particularly CFZ and SLI due to selection of Resistant Mutants. Of these patients, there may also be BDQ resistance in one-third (10%) as explained above. It needless to say that the prognosis for such patients with such an extensive pattern of Resistance (FQ, SLI, CFZ, BDQ) would be dismal. In context of India, even around 10% of MDR patients developing such an advanced pattern of resistance would translate into a huge number as Indian population is second highest in the World and India has one fourth of the world's MDR TB patients.

It is true that availability of CBNAAT in most districts would rapidly identify the R-resistant cases which need priority treatment both for the patient (lower morbidity and mortality) and the community (decreased transmission) but it may be wiser to empirically use a more robust regime consisting of a combination of drugs which will cover for potential FQ resistance till LPA results confirm FQ sensitivity after which patient may be safely put on Short-Course Regime.

## Conclusion

The aim of this article is not to create panic but only raise awareness about the potential risk of universal application of empirical treatment regime to the highly heterogenous disease pattern of Drug resistant Tuberculosis especially in context of a country like India. WHO regime is a very good option for eligible patients but if used inappropriately, it is likely to do more harm than good.

## References


1. World Health Organization. Global tuberculosis report. 2018.
2. World Health Organization. Treatment guidelines for drug-resistant Tuberculosis. 2016.
3. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR et al. Short, highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J RespirCrit Care Med. 2010; 182: 684-692.
4. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Lancet Respir Med. 2015; 3: 963-972.
5. Singhal P, Dixit P, Singh P, Jaiswal I, Singh M, et al. A study on pre-XDR & XDR tuberculosis & their prevalent genotypes in clinical isolates of Mycobacterium tuberculosis in north India. Indian J Med Res. 2016; 143: 341-347.
6. Jain A, Dixit P, Prasad R. Pre-XDR & XDR in MDR and Ofloxacin and Kanamycin resistance in non-MDR Mycobacterium tuberculosis isolates. Tuberculosis 2012; 92: 404-406.
7. Singh PK, Jain A. Limited Scope of Shorter Drug Regimen for MDR TB Caused by High Resistance to Fluoroquinolone. Emerg Infect Dis. 2019; 25:1760-1762.
8. Hartkoorn RC, Uplekar S, Cole ST. Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2014; 58: 2979-2981.
9. Almeida D, Ioerger T, Tyagi S, Li SY, Mdluli K, et al. Mutations in pepQ confer low-level resistance to bedaquiline and clofazimine in Mycobacterium tuberculosis. Antimicrobial agents and chemotherapy. 2016; 60: 4590-4599.
10. Ismail NA, Omar SV, Joseph L, Govender N, Blows L, et al. Defining bedaquiline susceptibility, resistance, cross-resistance and associated genetic determinants: A retrospective cohort study. EBioMedicine. 2018; 28: 136-142.