Editorial

For a long time, until the programmes started managing drugs resistant TB patients, the National Tuberculosis Control programmes were implemented for achieving good success rates for the patients infected with drug susceptible bacteria so that we are able to minimize the development of drug resistant strains. In addition, the programmes have been implemented on the premise that the drug resistance develops in two ways: Primary Drug Resistance or Acquired Drug Resistance. The main reasons for the acquired drug resistance being patient related issues like compliance or adherence, systemic issues like inadequate drug regimen or monotherapy, issue related to quality or supply of drugs or social issue like myths on the intake of Anti-TB drugs etc. Primary Drug resistance means the patient is infected with bacteria which are already resistant to drugs. The National Programmes adopted DOTS strategy which was expected to address the issues related to compliance, regimen or uninterrupted supply of good quality drugs. However, so far, the programmes have not been acknowledging or addressing issues other than conventionally thought causes for development of drug resistance. Effective first line treatment was expected to prevent emergence of drug resistance a s a public health measure. But the data suggest that primary transmission of drug resistant strains is now driving the spread of resistance including the high TB burden countries. It means the traditionally believed causes of development of drug resistance have now taken a back seat and the new emerging data indicates many other causes of development of drug resistance.

The prime way of development of drug resistance in M. tuberculosis is through mutations in genes encoding drug targets or enabling enzymes. The effect of drugs treatment is to diminish the population of drug susceptible bacteria which also enables the emergence of a strain able to bypass the treatment. Several studies in individual patients who have developed progressive drug resistance over time have documented the initial acquisition of isoniazid resistance as a result of one or more mutations, followed by acquisition of resistance to rifampicin or ethambutol (or both), pyrazinamide, and finally, the second-line and third-line drugs. When resistance to one or more drugs is acquired in this way, it is referred to as secondary resistance. By contrast, primary resistance occurs when resistant strains are transmitted to a new host in the same manner as a drug-susceptible strain.

Previous exposure to anti-tuberculosis drugs is consistently identified as a strong risk factor for MDR, but other host risk factors can vary in different geographical settings. The studies have proved that population younger than 65 years of age were 2.5 times more likely to have multi drug resistance than those above 65 years. A possible explanation for this is that older patients might have tuberculosis due to activation of a latent infection acquired before the emergence of drug resistance. Studies have not been able to conclusively prove HIV and Diabetes Mellitus as risk factors for drugs resistance.

The two deep rooted epidemiological beliefs of the Programme Managers are that resistance has a fitness cost rendering drug-resistant strains less transmissible and resistance is believed to primarily be acquired by patients who were previously exposed to anti-tuberculosis drugs. Consequently, for decades, tuberculosis control policies have targeted prevention of drug resistant tuberculosis through the WHO directly observed treatment, short course (DOTS) strategy and focused on detection of drug-resistant tuberculosis in individuals with a history of prior treatment for active tuberculosis (high-risk group). International policies have largely ignored patients who develop primary resistance. In most regions of the world, drug-resistant tuberculosis is now predominantly caused by transmission rather than acquisition of resistance, with an estimated 95·9% of MDR tuberculosis in new tuberculosis cases and 61·3% in previously treated cases being due to transmission.

Another important cause of acquired drug resistance had been attributed to poor adherence. Thus, acquired drug resistance was dealt with using a programmatic approach, specifically the DOTS strategy, to improve adherence. Emergence of acquired drug resistance eventually became equated with poor adherence, and high rates of acquired drug resistance were considered to be an indicator of poor performance of DOTS programmes. Indeed, careful historical documentation has shown that the problem of M tuberculosis acquired drug resistance arose as soon as drug therapy first became available, and has continued being a problem from the 1950s to the present. In 1970, Hugo David performed fluctuation tests to identify M tuberculosis mutation rates, and identified average mutation rates (as mutation per bacterium per generation) of $2 \cdot 56 \times 10^{-8}$ for isoniazid, $2 \cdot 56 \times 10^{-7}$ for ethambutol, and $2 \cdot 25 \times 10^{-10}$

for rifampin. The probability of acquired drug resistance to two or more drugs is the product of these mutation rates, so the probability of acquired drug resistance for these three drugs in combination would be ~1·0×10− [25]. In view of such low probability, it was thought that resistance could develop due to inadvertent monotherapy due to wrong prescription practices, issue related to drug supplies or poor patient adherence. Four scenarios were proposed for inadvertent monotherapy. First, given the high bacillary burden in which mutants probably pre-existed, and that each antibiotic in the combination only works on specific metabolic subpopulations of the bacteria (eg, isoniazid is the only effective drug against rapidly growing bacteria; thus, monotherapy is effectively being given), isoniazid resistant mutants would be selected if patients took the combination treatment for 2 days and then stopped. The second mechanism would arise during the sterilizing effect, given that pyrazinamide would be the only effective drug for semi-dormant M tuberculosis under acidic conditions, and rifampicin for non-replicating persistent bacteria under hypoxia; mathematical models predicted that poor compliance would lead to acquired drug resistance in this situation. The third mechanism involves regrowth during sub-inhibitory concentrations of drugs, especially for drugs (such as isoniazid) that have a high therapeutic margin and a long half-life because they remain present in the body after the clearance of other drugs. This is essentially a version of the pharmacokinetic mismatch hypothesis. The fourth scenario involves differential bacteriopausal mechanisms in which a drug such as rifampicin, whose post-antibiotic effect is shorter than of a companion drug such as isoniazid, selects isoniazid-resistant mutants during regrowth. In the standard anti-tuberculosis regimen, rifampicin and isoniazid both have a short half-life of 2–3 h and pyrazinamide has a half-life of 10 h, while M tuberculosis has a doubling time of 14–96 h and the mutation rates ($2{\cdot}56\times10^{-8}$ for isoniazid, $2{\cdot}56\times10^{-7}$ for ethambutol, and $2{\cdot}25\times10^{-10}$ for rifampin) identified by David, with a total bacterial burden of 10^8 in a cavity. The antibiotics are no longer present because clearance occurs before a single M tuberculosis has replicated, and certainly by the second and third replications. This timing makes the probability of generation of mutants, or even amplifying pre-existing ones, less likely, particularly for non-replicating persistors and semi-dormant bacilli, aptly described as “fat and lazy” by Garton and colleagues. The three meta-analyses conducted, were concordant in showing that supervised therapy was effective in reducing non-adherence and improving treatment completion. The meta-analyses also showed that no benefits were associated with DOTS compared with self-administered therapy when microbiological failure and relapse were examined as clinical endpoints. The incidence of acquired drug resistance was the same whether supervised therapy was given at home, in a health facility, by a family member, or by a community health-care provider.

Hollow fibre studies in tandem with in-silico clinical trial simulations predicted that, given the xenobiotic metabolism patterns in the Western Cape in South Africa, a proportion of patients would actually be on monotherapy despite being given the full multidrug regimen and being part of a DOTS programme. This is because of the differential rapid elimination of some drugs in the regimen, leading to prolonged monotherapy with the drug that is not rapidly or extensively metabolised over tens to hundreds of rounds of bacterial replication. The in-silico study predicted that 0·68% of patients would develop acquired drug resistance and MDR tuberculosis within 2 months despite 100% adherence, because of such differential pharmacokinetic variability of regimen components. Acquired drug resistance, including MDR tuberculosis, was encountered in 0·7% of patients during the first 2 months, despite adherence to standard doses of isoniazid, rifampicin, pyrazinamide, and ethambutol. All cases of acquired drug resistance, including MDR tuberculosis, were preceded by suboptimal drug concentrations due to pharmacokinetic variability. A meta-analysis of 13 randomised studies with 1631 rapid isoniazid acetylators and 1751 slow acetylators showed that rapid acetylators had 2·0 times higher occurrence of microbiological failure and acquired drug resistance compared with slow acetylators.

Dheda and colleagues have proposed and tested further pharmacokinetic variability at the level of drug penetration into tuberculosis lesions, which is dependent on the architecture of the tuberculosis lung cavity, for more than eight drugs. The lung cavity and surrounding fibrosis, depending on the size, will create a physicochemical barrier to drug entry, leading to anatomical site-based monotherapy. The programmatic level issues with drugs can also lead to pharmacokinetic variability and resulting monotherapy. In addition, health-care workers might prescribe lower doses than those needed to achieve the required optimal drug concentrations because of error or weight-based capping dosing practices (when dosing is capped at a particular maximum for the individual patient weight), which are often used in tuberculosis programmes, especially when fixed-dose formulations are given.

The role of efflux pumps in antibiotic resistance: As part of the bacterial stress reaction to the suboptimal antibiotic concentrations—and to effective monotherapy—efflux pumps in the bacilli are upregulated within hours. This

increase can be demonstrated by quantifying transporter messenger RNA, and is followed within a few days by phenotypically demonstrable low-level resistance that is reversed by efflux pump inhibitors such as verapamil. This efflux pump-dependent low-level resistance process allows the bacteria time to undergo multiple rounds of replication under suboptimal antibiotic pressure or monotherapy, allowing for development of mutations in the canonical drug resistance genes, in efflux pump genes, or in negative regulators of efflux pumps. The mutations in efflux pump regulators lead to high-level resistance, usually to multiple antibiotics. Indeed, mathematical modelling predicted a probability of the emergence of resistance to both isoniazid and rifampicin of 1×10^{-5} to 1×10^{-4} before commencement of therapy, suggesting that prior existence of MDR might be common. These patients would have a mixture of both drug-susceptible M tuberculosis and drug-resistant M tuberculosis that have arisen from a single strain.

Preclinical studies, prospective clinical studies, and meta-analyses have not identified the role of adherence in acquired drug resistance, contrary to common beliefs.Hence, the time is ripe that the Programmes start dealing with the individual drug resistant TB patients and identify those who require specialized care in view of the new emerging causes of drug resistance.

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