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Editorial

Drug-resistant tuberculosis: Promising progress with a note of caution

The management of drug-resistant tuberculosis (DR-TB) has been a formidable challenge for patients, healthcare providers and public health systems for many years. In particular, for multidrug-resistant TB (MDR-TB), resistant to both rifampicin and isoniazid, the available treatments have historically been prolonged, toxic, of poor efficacy, with a limited evidence base and often requiring an expensive individualized hospital-based approach. However, in recent times, many of these challenges have begun to be addressed. New drugs and a strengthening evidence base are enabling the development of shorter, more effective regimens with the potential for easy programmatic translation. Diagnostics have been revolutionized by the widespread introduction of molecular testing and care is being increasingly decentralized away from the few specialist centres. This progress has been hard-won but could be easily lost as the emergence of resistance to new drugs is inevitable. Here, we outline some of the key points of progress in the management of drug-resistant TB and areas still to be addressed to reduce the impact of drug-resistant TB.

Acquired drug resistance was a feature of the very first streptomycin trial in 1948 where resistance was demonstrated in 35 of 41 (85%) patients and was associated with poor outcomes[1]. When streptomycin was combined with isoniazid, rates of acquired resistance to both drugs dropped dramatically establishing the need for combination therapy in TB. In 1955/1956 the British Medical Research Council (MRC) conducted one of the first-ever national drug resistance surveys. Resistance to streptomycin was found in 2.5 per cent, to para-aminosalicylic acid (PAS) in 2.6 per cent and to isoniazid in 1.3 per cent of the 974 samples cultured; resistance to two or three drugs was rare[2]. This finding prompted the introduction of a third drug in the initial intensive phase to reduce the possibility of emergence of resistance among patients effectively receiving monotherapy if they were infected with a resistant strain.

Following the discovery of rifampicin and the demonstration of its promising bactericidal and sterilizing activity in both *in vitro* and mouse studies, the MRC embarked on a programme of short-course chemotherapy studies. A regimen based on six months of rifampicin and isoniazid was found to be as effective as the standard treatment of 18 months or more[3]. The development of drug resistance in patients relapsing post-treatment was rare and initial resistance to isoniazid appeared to have only a limited effect on the occurrence of failures during treatment or relapses post-treatment provided rifampicin had been given for at least four months. There was however, a high failure rate in the presence of initial resistance to both isoniazid and rifampicin. Subsequent studies demonstrated that efficacy in patients with mono-isoniazid resistance was also inferior to those with fully drug-susceptible TB disease[4].

Concerns came to the fore in the 1990s when the WHO began to report outbreaks of MDR-TB in different regions of the world which they attributed to 'inappropriate use of essential anti-tuberculosis drugs'[5]. Between 1984 and 1991 in New York city incidence rates of tuberculosis increased from 23 to 50/100,000/yr. The percentage of cases resistant to at least one drug rose from 19 per cent in 1987 to 28 per cent in 1991, while MDR-TB rose from six to 14 per cent. The reason for the increase in drug resistance was attributed to very poor adherence to treatment[6]. The epidemic was brought under control; probably the most important factor was expanded use of directly observed treatment.

At a similar time in the countries formerly part of the Soviet Union, the spread and establishment of

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drug-resistant strains of TB was enabled by a weakened public health system with poor treatment completion and outcomes. Eastern European and Central Asian countries still have the highest proportion of MDR-TB cases[7]. In India, the treatment of drug-susceptible disease with intermittent regimens was demonstrated to be a likely cause of increased acquired resistance to rifampicin and has now largely been abandoned[8]. Data from field studies conducted at the ICMR-National Institute for Research in Tuberculosis (NIRT) and National Tuberculosis Institute have shown comparatively little change in resistance rates in India over recent years[9,10]. Surveys conducted before 2012 showed a prevalence of between one and three per cent for MDR-TB in treatment naïve patients compared to 12 per cent in treatment-experienced patients[10]. The National Drug Resistance Survey conducted five years later revealed a similar picture with 2.8 per cent primary drug resistance and 11.6 per cent having acquired resistance[11]. A study from NIRT conducted in 2012 showed that among previously treated patients, MDR-TB was the highest among treatment failures (35%), followed by relapses (13%) and treatment after default (10%). The same study reported 10 per cent levels of resistance to ofloxacin among treatment-naïve patients[12].

Historically, it was recommended that patients with MDR-TB should be treated with lengthy individualized treatment strategies preferably initiated in the hospital, but this was realistically possible only in settings where there were good affordable laboratory facilities, criteria unmet in most low-income countries. In the 1990s Van Deun *et al*[13] initiated the first of a series of cohort studies in Bangladesh using standardized regimens. Their objective was to find an affordable, effective and safe regimen for a programmatic setting, considerably shorter than the 20 or more months' treatment that was being recommended at that time. Results from the sixth cohort of 204 patients were published in 2010 and demonstrated that in the Bangladesh setting, patients given a nine-month seven drug regimen had a favourable outcome approaching 90 per cent at 24 months, according to the current WHO classification[13]. No new drugs were included in the regimen which limited use of or excluded drugs likely to be poorly tolerated with the focus on reducing the risk of acquisition of additional resistance during treatment.

The results of this study elicited a mixed response, but there was recognition of the need to assess this regimen's efficacy in other settings, not least in populations coinfected with HIV. The STREAM Stage 1 trial, conducted in Ethiopia, South Africa, Vietnam and Mongolia demonstrated that the nine-month regimen was as effective as the 2011 WHO recommended regimen of 20 or more months' duration[14].

The availability of bedaquiline and other new and repurposed drugs such as pretomanid, delamanid and linezolid has meant that after more than 40 years effective injectable free regimens for MDR-TB are finally becoming a possibility. Combinations of these drugs are being evaluated in a number of studies and trials such as ZeNix, PRACTECAL and end TB[15]. New recommendations are expected from WHO later this year (in 2022) on what the future programmatic approach to treat MDR-TB should be.

This progress has been slow and hard-won. In order not to squander it further advances are needed. With multidrug therapy, acquired resistance arises if a patient is effectively only receiving monotherapy due to sub-inhibitory levels for the other drugs either as a result of the baseline resistance profile or reduced drug concentration due to poor absorption or adherence[16]. This is particularly relevant while bacillary burden is high. Randomized control trials that focus on the efficacy and toxicity of different regimens are not powered sufficiently to determine differences in the propensity of regimens to pre-dispose to acquired drug resistance. In addition, outcomes in the controlled environment of a trial often differ in programmatic settings[17]. Logically, regimens with fewer drugs in settings without adequate drug susceptibility testing will be more susceptible to acquired resistance emerging. On the other hand, additional drugs increase toxicity and pill burden, both of which can result in poor adherence, another driver of acquired resistance. A cautious approach is therefore needed when determining what should be implemented in guidance and surveillance for emerging resistance is crucial.

Molecular diagnostics and drug susceptibility testing have revolutionized our approach towards DR-TB management. Although culture-based methods have improved over time these have a turn-around time measured in weeks or months due to the intrinsic slow growth of *Mycobacterium tuberculosis* (Mtb). In addition, the personnel and laboratory requirements have meant that for many countries routine resistance testing was not available. Primary molecular testing for Mtb with cartridge-based nucleic acid amplification tests (CB-NAAT) that detects rifampicin resistance (RR)

has dramatically reduced the time for identification and treatment of MDR/RR-TB. Since 2019, bedaquiline and linezolid have formed the backbone MDR therapy in WHO guidance[18]. However, a survey of 5036 isolates from bedaquiline-naïve MDR patients from 11 countries including India between 2015 and 2019 showed that primary bedaquiline resistance was already present in 0.6 per cent, linezolid resistance in 1.5 per cent and co-resistance in 0.1 per cent of isolates[19]. The molecular basis for resistance to these drugs, along with delamanid and pretomanid, is still poorly defined meaning we will now be reliant again on phenotypic testing to determine resistance to these drugs. Hence, it is a clear priority to both strengthen laboratory capacity to ensure high-quality culture-based drug susceptibility testing is still available along with continuing research to determine the molecular basis of resistance for new drugs.

Although, first-line rapid molecular testing for rifampicin resistance is well established, first-line molecular testing for isoniazid resistance by contrast is not widely incorporated. Data from the latest Indian National Drug Resistance Survey however, showed isoniazid mono/polyresistance to be present in 11 per cent of new cases[20]. The Indian National TB Elimination Programme is rapidly replacing smear testing with NAAT leading to significant improvement in detection of MDR-TB. In 2019, 66,255 cases of MDR-TB were diagnosed which represented 84 per cent of the national target whereas only 16,067 cases of isoniazid mono/polyresistance were diagnosed, just 16 per cent of the national target[21,22]. There is increasing evidence that isoniazid mono-resistant strains are more likely to develop into multidrug resistance and that clinical outcomes are worse if undiagnosed. The molecular basis of isoniazid resistance is well described and could easily be incorporated into first-line CB-NAAT with clear benefit[23].

Transmitted resistance is most effectively prevented by a combination of active case finding with adequate resistance testing to find and effectively treat cases early and administer preventive therapy for contacts. Standardized options for preventive therapy in drug-resistant TB contacts are limited and as yet there are no completed trials in this population. Ongoing prevention trials include V-QUIN and TB-CHAMP which are assessing the role of levofloxacin versus placebo and the PHOENIx MDR-TB trial assessing delamanid versus isoniazid[24].

It has been particularly encouraging to observe the enhanced efforts being made in recent years to diagnose and treat drug-resistant tuberculosis as well as measures to prevent both acquired and transmitted resistance. However, we must accept that drug resistance cannot be simply eliminated and where there are weaknesses in the health system it will thrive. There is no cause for complacency and it will be essential to remain vigilant to continue to monitor both primary and acquired resistance levels.

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