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PERSPECTIVE

A poor drug-resistant tuberculosis programme is worse than no programme: time for a change

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TUBERCULOSIS (TB) services aim to prevent the transmission of TB through early diagnosis of infectious TB patients and rendering them non-infectious by effective treatment. Keeping TB patients alive by treatment but failing to cure them would promote the spread of TB in the community. Achieving a high proportion of treatment success is a fundamental principle in the development of the internationally recommended DOTS strategy.[1–3] The same principle should be applied to the management of multidrug-resistant TB (MDR-TB). Unfortunately, recent global reports on the outcome of programmatic management of drug-resistant TB (PMDT) show that most national tuberculosis programmes (NTPs) have not been able to achieve a high proportion of treatment success among MDR-TB patients.[4–9] This is a worrying situation that requires urgent remedial action.[10]

A poor programme is worse than no programme

In 1964, the World Health Organization (WHO) made recommendations on the development and implementation of an NTP.[11] A few years later, Grzybowski and Enarson assessed the fate of TB patients in different settings.[12] In India, follow-up of a cohort of smear-positive and culture-positive patients over 1.5 years revealed that 25% died, 43% remained bacteriologically positive and 32% became bacteriologically negative; after 5 years, 49% had died, 18% had remained bacteriologically positive and 33% had become bacteriologically negative.[13] In England, a 4-year follow-up of a cohort of TB patients revealed that 55% died, 19% remained bacteriologically positive, and 26% became bacteriologically negative.[14] The outcomes of TB treatment under programme conditions in several developing countries were assessed and were shown to be unsatisfactory. In Taiwan, in 1962, the 2-year outcome of a cohort of treated TB patients was 13% mortality, with 26% remaining bacteriologically positive and 62% becoming bacteriologically negative; the respective figures in Korea in 1968 were 11%, 26% and 63% (Figure 1). While chemotherapy under these programme conditions reduced the proportion of TB patients who died, a substantial proportion of patients remained bacteriologically positive. It was concluded by Grzybowski and Enarson, in their article published in 1978, that 'it was far better to do nothing than to treat the cases badly'.[12,15]

International Union Against Tuberculosis and Lung Disease collaborative programmes

These data were presented to and discussed at length within the Tuberculosis Surveillance Research Unit (TSRU). The recognition that 'poor treatment is worse than no treatment' inspired Karel Styblo (Director of the TSRU) to focus on the outcome of treatment in the collaborative programmes of the International Union Against Tuberculosis and Lung Disease (IUATLD, now known as The Union),[16] which were initiated in Tanzania in 1979 and subsequently expanded to Malawi, Senegal, Mozambique, Benin, Nicaragua, Yemen, Mali and Kenya.[15] The regimen used to treat new tuberculosis patients initially lasted 12 months. The outcome of treatment was not satisfactory (56% success rate), largely because a very high proportion of patients was lost to follow-up.[1] The introduction of an 8-month short-course regimen resulted in an increased rate of treatment success (>80%), and left very few smear-positive transmitters (Figure 1).[1] The most important factor explaining the increase in treatment success was a reduction in the proportion of patients lost to follow-up.[15] Subsequently, the strategy of the IUATLD collaborative programmes was adopted by the WHO to formulate a new global TB control strategy under the brand name DOTS.[2,3]

The challenge of multidrug-resistant tuberculosis

According to a series of WHO Global Tuberculosis Control Reports,[4–9] the proportion of successfully

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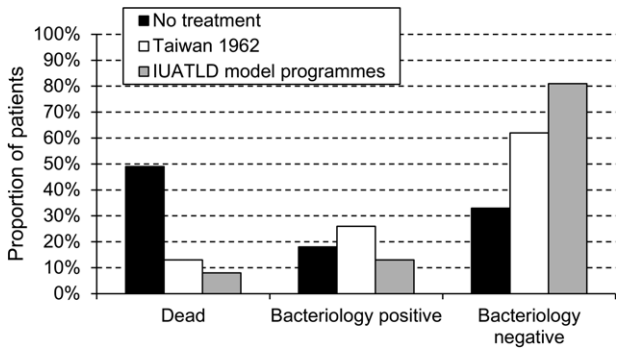

Figure 1 Fate of tuberculosis patients who had no treatment,[13] who were treated under programme conditions in Taiwan in 1962,[12] and who were managed in the International Union Against Tuberculosis and Lung Disease (IUATLD) model programmes.[1]

treated MDR-TB patients in most countries was <60%. The overall proportion of treatment success of the 2009 cohorts of MDR-TB was 48%, and the proportions of loss to follow-up/outcome not evaluated (28%) and failure (10%) were high.[9] This indicates that the duration of the infectious period might be prolonged by ineffective treatment, and that the transmission of even more resistant MDR-TB was likely to have been promoted. To achieve the vision of the Stop TB Strategy—a TB-free world—this must change.

In 2011, the WHO published updated recommendations on the management of drug-resistant TB, recommending an intensive phase of at least 8 months' duration and a total treatment duration of at least 20 months for MDR-TB patients who had not previously received second-line treatment.[17,18] Both are conditional recommendations made on the basis of very low quality evidence derived from an individual patient data (IPD) meta-analysis.[19] The overall outcome of treatment of patients included in the IPD meta-analysis was unsatisfactory: 54% were treated successfully, 8% failed or relapsed, 15% died and 23% were lost to follow-up (Figure 2).[19] The updated recommendations focused heavily on efficacy guided by odds ratios and recommendations for treatment duration based on the analysis of those who did not die or were not lost to follow-up. The effectiveness and feasibility of the recommended regimens in the field were thus barely taken into consideration, as losses to follow-up and deaths were ignored. The recommended regimens rely heavily on highly toxic second-line drugs which lack power and have many adverse effects. Studies have shown that 20–50% of MDR-TB patients require removal of drugs from their treatment regimens.[21] The challenge of frequent adverse drug effects is further complicated by the long duration of treatment,[22] which is difficult to manage in most resource-limited settings. Treatment interruption is frequent, particularly if patients are left alone to face the problems of taking these toxic drugs without adequate treatment support.

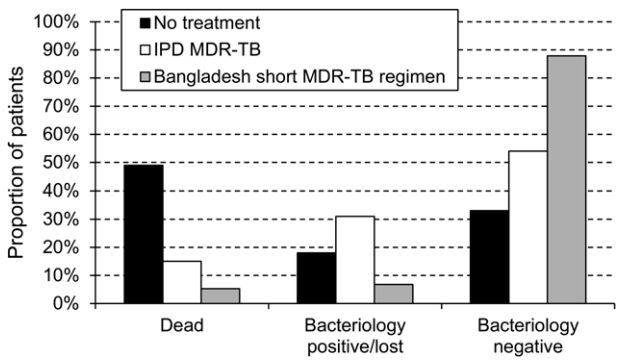

Figure 2 Fate of tuberculosis patients who had no treatment,[13] MDR-TB patients who were included in an IPD meta-analysis,[19] and MDR-TB patients treated with a Bangladesh short-course MDR-TB regimen in Bangladesh.[20] IPD = individual patient data; MDR-TB = multidrug-resistant tuberculosis.

To avoid loss to follow-up, strong, effective treatment support must be provided in the application of the current WHO-recommended long-duration MDR-TB regimen. This is only possible if resources are available. In Taiwan, thanks to a substantial investment by the government in socio-economic interventions and psychosocial support to MDR-TB patients, the proportion of loss to follow-up has been reduced to a minimum.[23] However, this will remain a difficult task in developing countries, where resources are limited.

Short MDR-TB regimens

In countries where the proportion of loss to follow-up has been high (>10%), the short-course MDR-TB treatment regimen piloted in Bangladesh and West Africa is probably the best option.[20] The so-called 'Bangladesh regimen' consists of high-dose gatifloxacin, clofazimine (CFZ), pyrazinamide and ethambutol throughout, supplemented by kanamycin (KM), prothionamide (PTH) and high-dose isoniazid (INH) in the intensive phase. The treatment duration of the intensive phase was 4 months, and was extended until sputum smear conversion; the duration of the continuation phase was 5 months. The treatment success rate in a cohort of 206 patients enrolled in 2005–2007 was 87.9% (Figure 2), and that in an expanded cohort of 476 MDR-TB patients not previously treated with second-line drugs was 86.1%.[24] Of 466 patients who underwent drug susceptibility testing (DST) for second-line drugs, 53 (11.4%) were resistant to ofloxacin (OFX) and two (0.4%) also to KM. During post-treatment follow-up, three (0.7%) of 410 successfully treated patients relapsed. Initial resistance to OFX and KM were significantly associated with failure and relapse. Of the eight patients with an unfavourable outcome, one acquired KM resistance in addition to initial resistance to all drugs in the regimen except CFZ; no other amplification of resistance was found.[24]

The short-course MDR-TB regimen is more easily implemented, better tolerated and capable of curing the large majority of the increasingly numerous drug-resistant cases remaining from previous first-line drug regimens, without striving for an unrealistic 100% efficacy. It maximises the use of the most powerful TB drugs, INH and the fourth-generation fluoroquinolones, which also have a large therapeutic margin. These are maintained even in the presence of documented drug resistance, due to the fact that for these drugs the minimal inhibitory concentration of most resistant mutants remains below drug tissue concentrations that can be achieved by a moderately elevated dose that is still well tolerated. More toxic drugs are avoided (para-aminosalicylic acid [PAS] and cycloserine) or used for a limited period (PTH and the second-line injectables) when they are necessary, to avoid the selection of fluoroquinolone-resistant mutants, thus reducing the risk of loss to follow-up. Limited use of these injectables with early declaration of failure also limits the amplification of more serious resistance and the creation of extensively drug-resistant tuberculosis (XDR-TB), even in cases resistant to most of the other drugs. More extensive experience in Bangladesh indicates that about 70% treatment success can be achieved even in the presence of initial fluoroquinolone-resistant MDR-TB, with only a moderately increased risk of failure and relapse, and rare progression of pre-XDR patients to XDR-TB.[23] The inclusion of CFZ may be an additional factor that explains the exceptionally rapid conversion and low relapse rate with this regimen.

Given the short duration of treatment, concerns have been voiced about the increased risk of relapse. The MDR-TB regimen piloted in Cameroon has therefore extended the total treatment duration to 12 months, with PTH throughout.[25] Of the 88 patients enrolled in 2008–2010, the cure rate was 92%. Over a total of 636 patient-months of follow-up after treatment, no relapse was observed. Kuaban et al. concluded that that a standardised short-course regimen may be the best pragmatic alternative for MDR-TB patients in resource-poor settings with little exposure to second-line anti-tuberculosis drugs.[25]

A practical combination of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) and the Union-recommended short-course MDR-TB regimen may have great potential in controlling MDR-TB in resource-limited settings (Figure 3). Among those with a high pre-test probability of rifampicin (RMP) resistance, no confirmation of RMP resistance is ever needed, and as INH is always included in the Union-recommended MDR-TB regimen, DST is not required to determine INH susceptibility. Among those with a low pre-test probability of RMP resistance, the positive predictive value (PPV) of RMP resistance by Xpert was too low in the early evaluations, and required confirmation.[26] For a confirmatory test

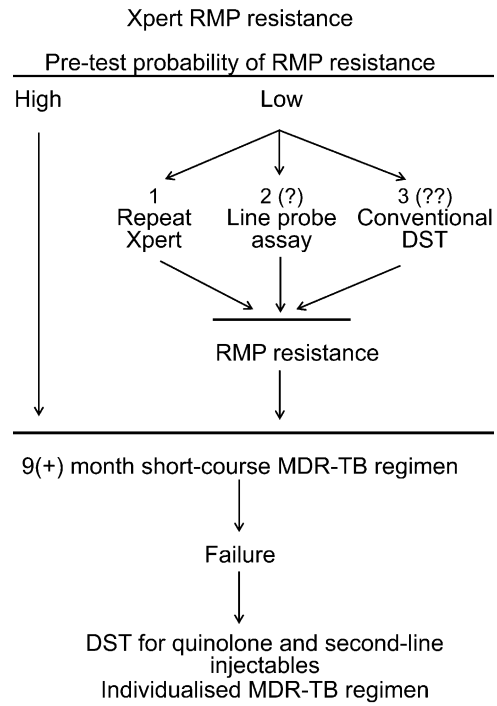

Figure 3 Practical algorithm for the use of Xpert® MTB/RIF and short MDR-TB regimen. RMP = rifampicin; DST = drug susceptibility testing; MDR-TB = multidrug-resistant tuberculosis.

performed on patients with RMP resistance detected by the first Xpert test, the pre-test probability and thus the PPV of RMP resistance of a follow-up test is very high. The most critical requirement is an ultra-short turnaround time, otherwise the utility of Xpert as the first screening test diminishes tremendously. Conventional DST as a confirmatory test is not an option, because the turnaround time is too long. The line probe assay (LPA) is sophisticated and is usually performed at a national reference laboratory. The turnaround time is likely to be long, as it involves the transportation of specimens. Furthermore, the current Genotype® MTBDRPlus version 2 LPA (Hain Lifescience GmbH, Nehren, Germany) fails to detect RMP resistance more often than Xpert (AVD, unpublished data). LPA is therefore also unlikely to be a satisfactory option unless a less sophisticated version, on a par with Xpert in terms of sensitivity and specificity, is developed. If Xpert is placed at the right location without the need for long-distance transportation, the repetition of Xpert on a different sputum sample is probably the best option as a confirmatory test.

A randomised control trial comparing a short-course MDR-TB regimen with WHO-recommended long-duration regimens has recently been launched, but the results will not be available until 2016 at the earliest. There are at least three reasons why we should not wait for the results of the trial and why we should encourage countries to pilot short-course MDR-TB regimens under proper conditions. First, it

has been reported in several settings that MDR-TB patients might refuse treatment because the treatment duration is long and the drugs are toxic. Short-course MDR-TB regimens offer an alternative, life-saving option that might be acceptable to patients.

Second, the long duration MDR-TB regimen is too demanding in terms of resources, and greatly overstretches the capacity of NTPs in resource-limited settings, as was demonstrated by the slow pace in scaling up PMDT and a high proportion of loss to follow-up among enrolled MDR-TB patients; short MDR-TB regimens offer a cheaper and more feasible alternative.

Third, fluoroquinolones will be widely used in the worldwide scale-up of PMDT, including countries that have so far had limited exposure to second-line drugs. Fluoroquinolone-resistant MDR-TB might thus increase in a few years' time in countries that previously had limited exposure to second-line drugs, and the window of opportunity to use short MDR-TB regimens might be closing rapidly. The intensive phase of short MDR-TB regimens consists of seven drugs, including a high-dose fluoroquinolone, and is extended until sputum conversion, thus minimising the risk of amplification of drug resistance. The possibility of a high frequency of relapse was not observed in Bangladesh or Cameroon and, should it occur, may be manageable by salvage individualised MDR-TB regimens. Even with a recurrence rate as high as 10%, short-course MDR-TB regimens would still greatly outperform the WHO-recommended MDR-TB regimens in most settings, which have a success rate of <60%.

Global control of MDR-TB should not be guided by statistical odds ratios alone; effectiveness and feasibility must be taken into consideration in the development of international strategy and national policies.

The WHO has endorsed the use of short MDR-TB regimens in projects that adhere to the following criteria: 1) approval of the project by a national ethics review committee, 2) delivery of treatment under operational research conditions in accordance with international standards, and 3) monitoring of the MDR-TB programme that is using short regimens, and of its corresponding research project, by an independent monitoring board.[9] Clearly, the Global Fund should not reject proposals aiming to pilot short MDR-TB regimens under proper conditions, and it should provide funding to support those countries interested in doing so. In the implementation of short-course MDR-TB regimens, strong treatment support should also be provided to patients, because these regimens are no less demanding than an 8-month first-line retreatment regimen. Failure of the short MDR-TB regimens could be declared as early as 6 months if there is a lack of response to treatment, thus reducing the risk of amplification of resistance.[27] An individualised regimen could be used as a salvage regimen in the small proportion of patients who fail the short-course MDR-TB regimens.

In conclusion, treatment of drug-resistant TB should aim for a high proportion of treatment success. Strong treatment support should be provided to all MDR-TB patients, regardless of the regimens used. Wide and careful application of the short-course MDR-TB regimen recommended by The Union has the potential for efficient and effective scale-up of PMDT. Leadership is needed at international and national levels to transform an unsatisfactory PMDT into an effective and successful one. The WHO's Global Tuberculosis Control reports in the next few years will show whether our generation will be able to make a difference in a timely manner.

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