1. Background and Rationale

Multi-drug resistant tuberculosis (MDR-TB) is a major global health problem threatening the gains made in TB control in the past 2 decades. In 2012, an estimated 450,000 people developed MDR-TB, of whom 170,000 died and only around 77,000 started treatment. Globally, only 48% of MDR-TB patients in the 2010 cohort were successfully treated. The question of whether we can further optimise treatment with current drugs to improve outcomes remains very relevant.1

In the absence of controlled trials, the number of drugs required to optimally treat MDR-TB remains controversial. Differing resistance patterns, patient factors (including nutritional status and co-morbidities), and efficacy of TB drugs complicate decisions around drug and regimen choice. A 2006 overview suggested that from a bacteriological perspective the use of 3 effective second-line drugs could be sufficient although in practice in humanitarian programmes and under national TB programme (NTP) conditions at least 4 effective drugs should be included.2 An individual patient meta-analysis of over 9000 patients found that use of 4 or more likely effective drugs in the intensive phase and 3 or more in the continuation phase were associated with higher adjusted odds ratios of treatment success in multivariate analysis.3 Current WHO guidelines recommend at least 4 effective drugs in addition to pyrazinamide in the intensive phase including an injectable and a higher generation fluoroquinolone with 2 group 4 drugs, and ethionamide (or prothionamide) and cycloserine preferred over para-aminosalicylic acid (PAS), although this is a conditional recommendation based on low quality evidence.4 However, some studies have suggested that more drugs might be better. In a retrospective cohort analysis from Latvia of 204 patients treated for MDR-TB in 2000, use of 5 or fewer drugs for 3 months or more was significantly associated with worse outcomes in a multivariate analyse.5

In a retrospective cohort study of 699 MDR-TB patients in Peru between 1999 and 2003, patients treated with an ‘aggressive regimen’ (containing at least 5 TB drugs including a fluoroquinolone and an injectable likely to be effective based on drug sensitivity testing [DST] and past treatment history and 4 TB drugs including a fluoroquinolone in the continuation phase) had a significantly lower risk of death in multivariate analysis.6

2. Research Question & Objectives

The study aimed to assess whether the use of an aggressive regimen was associated with reduced risk of death or treatment failure.

3. Methods & Results

The authors conducted a retrospective cohort study of consecutive patients initiating MDR-TB treatment between September 2000 and November 2004 in a single programme in Tomsk, Siberia, Russian Federation (http://en.wikipedia.org/wiki/Tomsk; more details of the programme can be found in a previous article). The programme was both a civilian and prison TB treatment programme. High rates of MDR-TB transmission have been reported previously in prisons in the region. TB diagnosis was via clinical, bacteriological and radiological criteria. Culture and DST to first and second-line drugs were performed in the Tomsk Oblast TB reference laboratory and the Massachusetts State Laboratory with appropriate methods. Individualised MDR-TB treatment regimens were administered according to standardised algorithms, including continued treatment with fluoroquinolones if ofloxacin resistance was demonstrated, and with capreomycin if there was resistance to kanamycin or amikacin regardless of whether resistance to capreomycin was demonstrated. An aggressive regimen was defined as containing at least 5 likely effective drugs during the intensive phase, followed by 4 during the continuation phase, with both a fluoroquinolone and an injectable agent in the intensive phase and a fluoroquinolone in the continuation phase. Drugs were defined as likely effective if all DST results prior to starting the regimen showed susceptibility; or, if no DST results were available, if the patient had not received the drug for at least 1 month. To account for drug changes during treatment, a month was classified as “a month of prescribed aggressive treatment” if at least 75% of regimen days met the definition. Standard definitions
for treatment outcomes were used. Potential predictors of the hazard of death or failure (low BMI, HIV status, co-morbidities, severe pulmonary disease, and severe clinical status) were included in a univariate and multivariate Cox proportional hazards analysis (for an example of this methodology see http://www.bmj.com/content/347/bmj.f4919). The model retained potential confounders if they changed the effect estimate of receipt of an aggressive regimen on death or failure by more than 10%, or if the a variable was expected to be a confounder based on clinical experience. Effect modification was assessed for XDR TB and previous fluoroquinolone or injectable use. Interactions, or effect modifications happen when the effects of a variable on an outcome are modified by a third variable. A sensitivity analysis was also performed with time to follow-up restricted to the same time, considering that person-time to follow-up differed between exposure groups.

6. Discussion
A total of 638 patients treated for confirmed MDR-TB were included. Most were male (83.2%). Current or previous incarceration was high at 56.8%, as expected given the inclusion of a prison treatment programme in the study. Alcohol use/dependence was reported in 42.8% and illicit drug use in 18.6%. Co-morbidities were high (70.4%) by the definition of the paper; however, HIV (0.8) and diabetes mellitus (4.1%) were low. History of previous treatment was high (99.5%), with high proportions of previous fluoroquinolone use (15%) and prior injectable exposure (30%). A high proportion of patients had severe disease (severe pulmonary disease 43.4%, severe baseline clinical status 58%), and bilateral cavitary disease were common (61.7%). Overall 81.8% received an aggressive regimen at some point, with treatment duration of a median of 19 months (IQR:18-23). Overall outcomes were: 62.4% cured, 3.8% treatment completed, 8.8% failure, 4.9% death and 20% default (note that newer guidelines suggest loss to follow-up is the preferable term). Of the negative outcomes, the 54 treatment failures and the 30 deaths during the observation period were included in the analysis as events.

The main findings were that the following factors were reasonably strong predictors of lower risk of death and failure: monthly receipt of aggressive MDR-TB regimen (multivariate hazard ratio 0.52; 95% CI 0.29-0.94) and more than 2 previous TB treatments (0.53; 95% CI 0.31-0.92). Severe baseline clinical status was a strong predictor of death and failure (2.68 95% CI 1.45-4.95). While the study is not novel in the sense that it is following a similar methodology to the analysis of aggressive treatment regimens in a retrospective cohort from Peru, it is valuable for trying to robustly analyse what remains a pressing issue for many MDR-TB programme managers for which there are few studies.

Some key limitations include the retrospective nature (although missing data looks limited), a definition of aggressive that may not take into account the impact of extra group 5 drugs in regimens (which could increase efficacy or could result in increased side effects or drug interactions resulting in worsened outcomes), and the lack of inclusion of an analysis of the impact of aggressive regimens on default or indeed poor outcomes overall. The authors do discuss the potential limitation of survival bias given that, in multivariate analysis, previous treatment more than 2 times for TB was associated with nearly similar prediction of reduced risk of failure and death as having an aggressive regimen.

Questions for discussion:

1) Is there any further information you would like to help you to draw your own conclusions?
2) Do you agree with the authors’ conclusions?
3) Do you think this paper will influence your clinical practice?

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http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001300