

## Long term efficacy of DOTS regimens for tuberculosis: systematic review

Helen S Cox, Martha Morrow, Peter W Deutschmann

### EDITORIAL by Davies and Squire

Australian International Health Institute, University of Melbourne, Carlton, VIC 3010, Melbourne, Australia

Correspondence to: H S Cox, Macfarlane Burnet Institute for Medical Research and Public Health, Melbourne, VIC 3004, Australia [hcox@burnet.edu.au](mailto:hcox@burnet.edu.au)

BMJ 2008;336:484-7  
doi:10.1136/bmj.39463.640787.BE

### ABSTRACT

**Objective** To identify published studies assessing tuberculosis recurrence after successful treatment with standard short course regimens for six months to determine the strength and sufficiency of evidence to support current guidelines.

**Design** Systematic review.

**Data sources** Medline, Embase, Cochrane clinical trials register, specialist tuberculosis journals, and reference lists. Only English language publications were eligible.

**Review methods** Studies were included irrespective of methodology or quality. Abstracted information included inclusion and exclusion criteria for participants, duration of follow-up, and definitions of treatment success and disease recurrence. The primary outcome was the proportion of successfully treated patients recorded with recurrent tuberculosis during the follow-up period.

**Results** 17 study arms from 16 studies met the inclusion criteria; 10 were controlled clinical trials and six were either studies done under programmatic conditions or observational studies from functioning tuberculosis programmes. Although several clinical trials supported the use of daily treatment regimens, studies reporting tuberculosis recurrence after intermittent regimens were limited. Few studies carried out under routine programmatic conditions reported disease recurrence. Overall there was wide variation in recurrence after successful treatment, ranging from 0% to 14%. Considerable heterogeneity across studies precluded the systematic assessment of factors contributing to tuberculosis recurrence.

**Conclusions** Despite DOTS (directly observed treatment, short course) being implemented for more than 10 years and millions of patients treated for tuberculosis, few studies have assessed the ability of standard DOTS regimens to result in lasting cure for patients treated under routine programmatic conditions.

### INTRODUCTION

The DOTS (directly observed treatment, short course) strategy for tuberculosis control was launched by the World Health Organization in 1995.<sup>1</sup> The strategy is based around short course treatment regimens for a minimum of six months. Patients are considered cured if they finish the treatment with negative sputum bacteriology. Those adjudged as completing treatment

have finished the regimen without evidence of treatment failure and without negative bacteriology. Despite being assessed as cured, patients can develop recurrent disease. This was thought to result from relapse of the same infection, but reinfection with a different strain of *Mycobacterium tuberculosis* is also an important cause.<sup>2,3</sup>

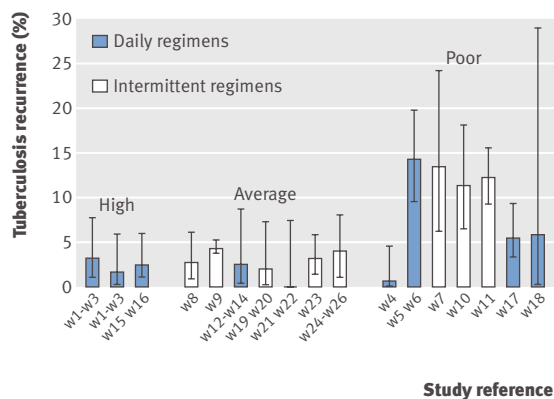
High rates of tuberculosis recurrence have been observed recently among patients reported as successfully treated within a DOTS programme in Uzbekistan.<sup>4,7</sup> Although drug resistance is high in this region and contributed significantly to disease recurrence and mortality in the study population, recurrence and mortality were also high (22%) among the small subgroup initially diagnosed as new patients with pan susceptible strains of tuberculosis, and seemingly successfully treated under DOTS. We carried out a systematic review of studies assessing tuberculosis recurrence after successful treatment with standard regimens for six months to determine the strength and sufficiency of evidence to support current guidelines.

### METHODS

The DOTS guidelines recommend a short course regimen for six months for newly diagnosed patients whose sputum shows smear positive results, starting with an intensive phase using isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, followed by a continuation phase of rifampicin and isoniazid for four months. When direct observation is not feasible, the DOTS strategy recommends a continuation phase for six months with self administered ethambutol and isoniazid.<sup>4,5</sup>

Under DOTS, treatment may be given daily or three times weekly for both phases. In the intensive phase ethambutol may be replaced by streptomycin.<sup>4</sup> The various potential alternatives for treatments lasting six months translate into eight different regimens. Two may be omitted on the assumption that programmes are highly unlikely to adopt an intermittent intensive phase followed by a daily continuation phase. We focus on tuberculosis recurrence among patients successfully treated with any of the six short course regimens recommended under DOTS (see [bmj.com](http://bmj.com)).

We searched three databases using combinations of several terms (see [bmj.com](http://bmj.com)) for studies using any of the



Tuberculosis recurrence after successful treatment (with 95% confidence intervals), divided by quality rating for treatment

six treatment regimens for pulmonary tuberculosis and determined rates of recurrence after treatment. We also manually searched the *International Journal of Tuberculosis and Lung Disease*, along with its precursors (see [bmj.com](#)), and identified studies through back tracing of reference lists and subsequent reports from the same longitudinal studies.

We abstracted information on treatment regimen, study design, country, year of patient enrolment, sample size, inclusion and exclusion criteria for participants, follow-up, HIV testing, testing of susceptibility to tuberculosis drugs, definitions of treatment success and recurrence, measures taken to maximise adherence, default rate during treatment, and whether recurrences were differentiated into those caused by relapse or those caused by reinfection.

For the assessment of recurrence we abstracted data according to the following criteria: new tuberculosis (no previous treatment for tuberculosis, or less than 2-4 weeks of previous treatment); HIV negative; drug susceptible tuberculosis (or without multidrug resistant tuberculosis); and bacteriological confirmation of treatment success. The primary outcome measure was the proportion of successfully treated patients who developed recurrent tuberculosis during follow-up.

We used the exact binomial method to calculate confidence intervals for recurrence. We assessed methodological quality across two domains. Firstly, we assessed the quality of the initial treatment episode through reported measures to ensure adherence and through default from treatment. Secondly, we assessed adequacy of follow-up to ascertain recurrence by the method used to trace patients (active or passive detection) and by the proportion of patients excluded from the follow-up analysis. Studies were classified as high, average, or poor in each domain according to several criteria (see box on [bmj.com](#)).

## RESULTS

Overall, 131 full text articles from 3432 identified citations were selected for review (see [bmj.com](#)). Of these, 102 were excluded. The remaining 29 articles corresponding to 19 studies were considered for

inclusion. A further three studies were excluded.<sup>5-7</sup> An additional study arm in one study<sup>w21 w22</sup> was excluded because the drugs were in a combined formulation and there were doubts as to the adequacy of some doses.<sup>8</sup> An Indian study was included despite the lack of a detailed description of the treatment regimen, as it could be assumed that the regimen followed the DOTS guidelines.<sup>w9</sup>

### Study characteristics

The 16 included studies (17 study arms) are summarised on [bmj.com](#).<sup>w1-w26</sup> Nine were controlled clinical trials and one was a prospective trial under conditions approximating those in routine programmes.<sup>w17</sup> The remaining six were observational studies.<sup>w5-w7 w9-w11</sup> Although at least one study arm was located for each of five of the regimens, only the Uzbekistan study<sup>w7</sup> investigated the commonly used regimen of ethambutol with an intermittent continuation phase.

### Tuberculosis recurrence

Levels of recurrence after successful treatment ranged from 0%<sup>w21 w22</sup> to 14%<sup>w5 w6</sup> (figure and [bmj.com](#)). The South African study was the only study to differentiate between relapse and reinfection as the cause of recurrence.<sup>w5</sup> Among HIV negative cases, 94% of recurrent episodes were attributed to relapse, whereas reinfection was more likely among HIV positive cases. High rates of recurrence were also seen in the observational studies carried out within DOTS programmes in India, a country that uses an intermittent regimen. Two of these studies reported recurrence of more than 10%.<sup>w10 w11</sup>

### Key differences between included studies

The quality of treatment according to the chosen indicators varied across studies (see [bmj.com](#)). Although not definitive, there was a tendency for higher recurrence rates among studies rated as poor for treatment (figure). High heterogeneity was also found in other key factors among the studies, including differences between the types of patients initially enrolled and then excluded from the analysis of recurrence. Many of the clinical trials restricted enrolment, excluding patients in poor clinical condition or with concomitant diseases (see [bmj.com](#)). In addition, some clinical trials recruited only easily accessible patients, excluding those in rural areas. In several of the clinical trials a tighter definition of default was used to exclude patients from the analysis of recurrence than is commonly used in the DOTS strategy (see [bmj.com](#)).

Variations were also found in measurement and reporting of HIV infection and the extent of resistance to tuberculosis drugs. Attempts were made to negate the potential influence of both factors by abstracting recurrence for HIV negative patients or those infected with drug susceptible strains when these data were given. Despite this, in several study arms these factors were not measured or not adequately reported on (see

bmj.com). Key differences also existed in definitions of treatment success; in general, the clinical trials defined success as bacteriological cure whereas many of the observational studies relied on the DOTS definition of treatment success, which includes patients who complete treatment without bacteriological confirmation of cure (see bmj.com).

Adequacy of assessment of recurrence also varied across study arms; five studies were rated as poor primarily because a high proportion of patients was excluded from the analysis of recurrence (see bmj.com). The impact of this exclusion is unclear, although studies relying on passive detection of recurrence are more likely to under-report recurrence than studies using active follow-up of patients. The definition of recurrence also varied across study arms, ranging from a strict standard of at least two positive cultures (at least 5-10 colonies) at least a month apart and within a three month period, to a clinical diagnosis of tuberculosis, with or without bacteriological confirmation (see bmj.com). Finally, the extent to which deaths were excluded or could be attributed to recurrent disease was also variably assessed, as was the duration of follow-up after treatment (see bmj.com).

## DISCUSSION

This review was prompted by a finding of high tuberculosis recurrence after successful treatment from a DOTS programme utilising a recommended short course treatment regimen for six months.<sup>w7</sup> We assessed whether evidence is sufficient that the regimens promoted through the DOTS strategy result in lasting cure. Several controlled clinical trials showed the effectiveness of daily regimens for six months under trial conditions but few reported on tuberculosis recurrence after the recommended intermittent regimens. Only a handful of assessments of post-treatment or longer term outcomes from functioning DOTS programmes was found.

### Potential contributors to tuberculosis recurrence

We found large variation in tuberculosis recurrence across the included studies, ranging from 0% to 14%. Several factors might explain this. The studies varied not just in quality and regimen used but also in inclusion and exclusion criteria, the presence of concomitant diseases, and definitions of treatment success and recurrence. Given the noticeable differences in key criteria between the included studies it was not possible to carry out a meta-analysis to assess the influence of individual factors on recurrence. None the less, the observed differences in recurrence may be explained by the key factors of daily compared with intermittent treatment, participants' characteristics, and poor adherence resulting from the difficulties of direct observation of doses.

The DOTS guidelines state that "isoniazid, rifampicin, pyrazinamide and streptomycin are all as efficacious when given three times weekly as when given daily."<sup>4</sup> The Cochrane database of systematic reviews, however,

concludes that evidence for this is insufficient, with only one study fulfilling their selection criteria.<sup>9</sup> A large case-control study from Hong Kong found intermittent treatment to be significantly associated with recurrence when compared with daily treatment, whereas prolongation of treatment was protective.<sup>10</sup>

Overall, potential contributors to recurrent tuberculosis after successful treatment include shorter durations of treatment (particularly rifampicin), poor adherence (mainly during the intensive phase), fewer than three drugs used in the intensive phase, greater disease severity and cavitation, high bacterial load, smoking, being male, concomitant disease, being underweight, and HIV infection.<sup>10-15 w11 w26</sup> Greater disease severity, difficulties with adherence, and concomitant diseases are commonplace in settings with a high burden of tuberculosis, which commonly are characterised by poverty, malnutrition, high rates of HIV infection, and poor access to health care. The differences in disease recurrence across the included studies might be explained by the setting, along with the exclusion from some studies of patients with factors most likely to contribute to recurrence.

Direct observation is particularly difficult, as it typically requires weak patients to expend time, energy, and money to attend health centres over long periods. When distance or difficult terrain present obstacles, direct observation of all doses and 100% adherence is unlikely, even among patients not classified as defaulting.

### Study limitations

The main limitations to this review were the small number of studies and heterogeneity. The heterogeneity precludes a more detailed analysis to explain differences in tuberculosis recurrence after successful treatment. The features that emerge as limitations for the review, together with the variation in recurrence reported, are themselves key findings, however, and underpin our call for detailed evaluation of tuberculosis programmes in high burden settings.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

WHO recommends that patients newly diagnosed with pulmonary tuberculosis be given a short course of treatment for six months, daily or intermittently, through the DOTS strategy

A proportion of patients redevelop disease after treatment stops; tuberculosis recurrence is a useful indicator of treatment efficacy

## WHAT THIS STUDY ADDS

A limited number of studies have assessed tuberculosis recurrence after successful treatment

The wide variation in recurrence rates suggests that treatment regimens recommended under DOTS may not be universally successful

Only one study differentiated relapse from reinfection with a different *M tuberculosis* strain after successful treatment. This study found that most recurrences among HIV negative patients were due to relapse.<sup>w5 w6</sup> Reinfection has been reported to account for up to 77% of disease recurrences, however, depending on the prevalence of tuberculosis in the community and the prevalence of HIV infection.<sup>3 16</sup> The extent to which reinfection contributes to the proportions of recurrence identified in this review is therefore unclear.

The lack of data on tuberculosis recurrence from developed countries for comparison might be considered a limitation. Although several studies from developed nations reported tuberculosis recurrence and even differentiated between relapse and reinfection, in general these studies report outcomes after a range of non-standardised regimens or use twice weekly intermittent regimens,<sup>16 17</sup> and are therefore not directly comparable to those in this review.

#### Implications of high tuberculosis recurrence

At present the effectiveness of interventions in controlling tuberculosis is determined by end of treatment outcomes and estimates of case detection. Countries that implement DOTS normally report patient numbers and outcomes annually to WHO. These figures are used to assess progress in control and to predict changes in incidence and prevalence.<sup>18 19</sup> The global targets set for tuberculosis control are to detect 70% of new sputum smear positive cases and to successfully treat 85% of these cases.<sup>20</sup> If, however, disease recurrence is substantial, current end of treatment targets may be too low to bring about the expected declines in incidence.

The rise of multidrug resistant tuberculosis and extensively drug resistant tuberculosis have prompted renewed calls for more effective drugs and newer shorter treatment regimens.<sup>21 22</sup> The results presented here suggest that any new regimens should undergo rigorous clinical trials and be trialled under routine programmatic conditions. These evaluations should also extend beyond the end of treatment and not only differentiate between relapse and reinfection but also consider the implications of coinfection with HIV.

Although the increase in tuberculosis cases is being fuelled by the HIV epidemic in Africa, factors such as poor case detection, a selective focus on smear positive patients, and, potentially, recurrent disease may be instrumental in Africa and elsewhere. The implementation of the DOTS strategy has improved the outcomes for millions of patients. However, treatment regimens that can only produce good outcomes reliably under “ideal” conditions may be of limited use in high burden settings, where challenges for the provision of even basic health services are manifold and complex.

**Contributors:** See [bmj.com](http://bmj.com).

**Funding:** HSC was supported by an Australian National Health and Medical Research Council PhD scholarship.

**Competing interests:** None declared.

**Ethical approval:** Not required.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

- 1 WHO. *WHO report on the tuberculosis epidemic, 1995. Stop TB at the source*. Geneva: WHO, 1995. Report No WHO/TB/95.183.
- 2 Chiang CY, Riley LW. Exogenous reinfection in tuberculosis. *Lancet Infect Dis* 2005;5:629-36.
- 3 Verver S, Warren RM, Beyers N, Richardson M, van der Spuy GD, Borgdorff MW, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. *Am J Respir Crit Care Med* 2005;171:1430-5.
- 4 WHO. *Treatment of tuberculosis: guidelines for national programmes*. Geneva: WHO, 2003. Report No WHO/CDS/TB/2003.313.
- 5 Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet* 2004;364:1244-51.
- 6 Algerian Working Group/British Medical Research Council. Controlled clinical trial comparing a 6-month and a 12-month regimen in the treatment of pulmonary tuberculosis in the Algerian Sahara. Algerian Working Group/British Medical Research Council cooperative study. *Am Rev Respir Dis* 1984;129:921-8.
- 7 Balasubramanian VN, Oommen K, Samuel R. DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State, India. *Int J Tuberc Lung Dis* 2000;4:409-13.
- 8 Iseman MD. Good news and not such good news. *Int J Tuberc Lung Dis* 1999;3:87.
- 9 Mwandumba HC, Squire SB. Fully intermittent dosing with drugs for treating tuberculosis in adults. *Cochrane Database Syst Rev* 2001;(4):CD000970.
- 10 Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. A nested case-control study on treatment-related risk factors for early relapse of tuberculosis. *Am J Respir Crit Care Med* 2004;170:1124-30.
- 11 Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis* 2003;37:101-12.
- 12 Benator D, Bhattacharya M, Bozeman L, Burman W, Cantazaro A, Chaisson R, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet* 2002;360:528-34.
- 13 Johnson JL, Okwera A, Vjecha MJ, Byekwaso F, Nakibali J, Nyole S, et al. Risk factors for relapse in human immunodeficiency virus type 1 infected adults with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1997;1:446-53.
- 14 Aber VR, Nunn AJ. [Short term chemotherapy of tuberculosis. Factors affecting relapse following short term chemotherapy]. *Bull Int Union Tuberc* 1978;53:276-80.
- 15 Banda H, Kang'ombe C, Harries AD, Nyangulu DS, Whitty CJ, Wirima JJ, et al. Mortality rates and recurrent rates of tuberculosis in patients with smear-negative pulmonary tuberculosis and tuberculous pleural effusion who have completed treatment. *Int J Tuberc Lung Dis* 2000;4:968-74.
- 16 Jasmer RM, Bozeman L, Schwartzman K, Cave MD, Saukkonen JJ, Metchock B, et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *Am J Respir Crit Care Med* 2004;170:1360-6.
- 17 Dutt AK, Moers D, Stead WW. Short-course chemotherapy for tuberculosis with mainly twice-weekly isoniazid and rifampin. Community physicians' seven-year experience with mainly outpatients. *Am J Med* 1984;77:233-42.
- 18 WHO. *Global tuberculosis control, surveillance, planning, financing*. Geneva: WHO, 2007. Report No WHO/HTM/TB/2007.376.
- 19 Dye C, Watt CJ, Bleed DM, Hosseini SM, Raviglione MC. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA* 2005;293:2767-75.
- 20 Dye C, Maher D, Weil D, Espinal M, Raviglione M. Targets for global tuberculosis control. *Int J Tuberc Lung Dis* 2006;10:460-2.
- 21 Raviglione M. XDR-TB: entering the post-antibiotic era? *Int J Tuberc Lung Dis* 2006;10:1185-7.
- 22 Hargreaves S. Existing tuberculosis drugs may hold the key to shorter treatment. *Lancet Infect Dis* 2007;7:309.

**Accepted:** 10 December 2007