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- 1 Child Health Research Project. *Special Report. Reducing perinatal and neonatal mortality. Report of a meeting*. Baltimore, MD: Child Health Research Project, 1999.

- 2 Lechtig A, Yarbrough C, Delgado H, Habicht JP, Martorell R, Klein RE. Influence of maternal nutrition on birth weight. *Am J Clin Nutr* 1975;28:1223-33.
- 3 Lechtig A, Habicht JP, Delgado H, Klein RE, Yarbrough C, Martorell R. Effect of food supplementation during pregnancy on birth weight. *Pediatrics* 1975;56:508-20.
- 4 Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM, et al. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *BMJ* 1997;315:786-90.
- 5 West KP Jr, Katz J, Khatri SK, LeClerq SC, Pradhan EK, Shrestha SR, et al. Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group. *BMJ* 1999;318:570-5.
- 6 Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol* 1996;87:163-8.
- 7 Ashworth A. Effects of intrauterine growth retardation on mortality and morbidity in infants and young children. *Eur J Clin Nutr* 1998;52 (suppl 1):S34-42.
- 8 Garner P, Kramer MS, Chalmers I. Might efforts to increase birth weight in undernourished women do more harm than good? *Lancet* 1992;340:1021-2.
- 9 Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. *J Nutr* 1994;124:645-54.
- 10 Solomons NW, Ruz M. Zinc and iron interaction: concepts and perspectives in the developing world. *Nutr Res* 1997;17:177-85.
- 11 Solomons NW. Competitive interaction of iron and zinc in the diet: consequences for human nutrition. *J Nutr* 1986;116:927-35.
- 12 Ramakrishnan U, Manjrekar R, Rivera J, Glonzales-Cossio T, Martorell R. Micronutrients and pregnancy outcome: a review of literature. *Nutr Res* 1999;19:103-59.

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## Impact of DOTS compared with DOTS-plus on multidrug resistant tuberculosis and tuberculosis deaths: decision analysis

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### Abstract

**Objective** This study sought to determine the impact of the World Health Organization's tuberculosis treatment strategy (DOTS) compared with that of DOTS-plus on tuberculosis deaths, mainly in the developing world.

**Design** Decision analysis with Monte Carlo simulation of a Markov decision tree.

**Data sources** People with smear positive pulmonary tuberculosis.

**Data analysis** Analyses modelled different levels of programme effectiveness of DOTS and DOTS-plus, and high (10%) and intermediate (3%) proportions of primary multidrug resistant tuberculosis, while accounting for exogenous reinfection.

**Main outcome measure** The cumulative number of tuberculosis deaths per 100 000 population over 10 years.

**Results** The model predicted that under DOTS, 276 people would die from tuberculosis (24 multidrug resistant and 252 not multidrug resistant) over 10 years under optimal implementation in an area with 3% primary multidrug resistant tuberculosis. Optimal implementation of DOTS-plus would result in four (1.5%) fewer deaths. If implementation of DOTS-plus were to result in a decrease of just 5% in the effectiveness of DOTS, 16% more people would die with tuberculosis than under DOTS alone. In an area

with 10% primary multidrug resistant tuberculosis, 10% fewer deaths would occur under optimal DOTS-plus than under optimal DOTS, but 16% more deaths would occur if implementation of DOTS-plus were to result in a 5% decrease in the effectiveness of DOTS

**Conclusions** Under optimal implementation, fewer tuberculosis deaths would occur under DOTS-plus than under DOTS. If, however, implementation of DOTS-plus were associated with even minimal decreases in the effectiveness of treatment, substantially more patients would die than under DOTS.

### Introduction

The current recommendation for initial treatment of tuberculosis includes the standard first line regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol. Since 1993 it has been recommended that treatment be given as part of a policy known as DOTS (directly observed treatment, short course; box).<sup>1</sup> However, outcomes are poor when patients who are infected with *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin (multidrug resistant tuberculosis) are treated with the standard regimen.<sup>2,3</sup> Reserve or second line antituberculosis drugs have therefore become components of an approach known as DOTS-plus (box).<sup>4</sup> Although reported to attain high rates of

success in patients with multidrug resistant tuberculosis,<sup>5,6</sup> the proposed widespread implementation of DOTS-plus has been controversial.<sup>7</sup>

Second line agents that would be used under DOTS-plus are more expensive, more difficult to administer, and often poorly tolerated. Our hypothesis is that the implementation of DOTS-plus might divert resources from DOTS, decreasing the effectiveness of DOTS. In addition, if DOTS-plus were to be implemented incompletely the bacterium could develop resistance to second line agents.

A randomised controlled clinical trial assessing the effectiveness of DOTS compared with that of DOTS-plus is unlikely ever to be conducted because of logistical and ethical concerns. We used decision analysis to compare the possible outcomes of the two treatment strategies and to assess the impact of varying levels of effectiveness.

## Methods

We analysed data for adults in the developing world who had smear positive pulmonary tuberculosis. Not enough data on the effectiveness of DOTS and DOTS-plus in HIV positive patients were available to be included in the analysis. We analysed DOTS and DOTS-plus for differing levels of effectiveness of the programmes, under conditions with moderate (3%) and high (10%) proportions of cases of incident multidrug resistant tuberculosis. We assessed the impact of the different treatment strategies by tabulating the cumulative number of tuberculosis deaths that occurred for each scenario over a period of 10 years.

## Model

We used a Monte Carlo simulation of a Markov model (figure) to perform the decision analysis.<sup>8</sup> For each scenario we followed a hypothetical cohort for 10 years, with a cycle length of one year. We defined the probability of each event for each cycle. For each analysis we performed 25 000 Monte Carlo simulations and expressed the cumulative number of tuberculosis deaths as the rate per 100 000 people during the 10 year period. To allow for a valid comparison between the different scenarios of treatment, and because the number of multidrug resistant and highly drug resistant outcomes was small, we used the same random sequence for all analyses.

## Probability estimates

We obtained probability estimates from articles published in peer reviewed journals identified through a Medline search and from global reports published by WHO. See [bmj.com](http://bmj.com) for tables showing estimates used for the analyses of optimal DOTS and DOTS-plus and their references.

The probabilities under optimal DOTS-plus differed from those under DOTS in that rates of survival and cure of patients with multidrug resistant tuberculosis were higher under DOTS-plus. In addition, patients treated under DOTS-plus receive second line agents and could therefore develop resistance to these drugs (and consequently develop highly drug resistant tuberculosis), but we assumed that patients treated under DOTS could not. For analyses of the optimal implementation of DOTS and DOTS-plus we used the baseline probabilities for survival and cure

## DOTS and DOTS-plus: treatment strategies for pulmonary tuberculosis in the developing world

### DOTS is a package of five points:

- Commitment of governments to a national tuberculosis programme
- Detection of cases through case finding by sputum smear microscopy examination of patients with suspected tuberculosis in general health services
- Standardised short course chemotherapy with the first line drugs isoniazid, rifampicin, pyrazinamide, and ethambutol (or streptomycin) for, at least, all smear positive cases of tuberculosis under proper conditions of case management
- Regular, uninterrupted supply of all essential antituberculosis drugs
- A monitoring system for programme supervision and evaluation.

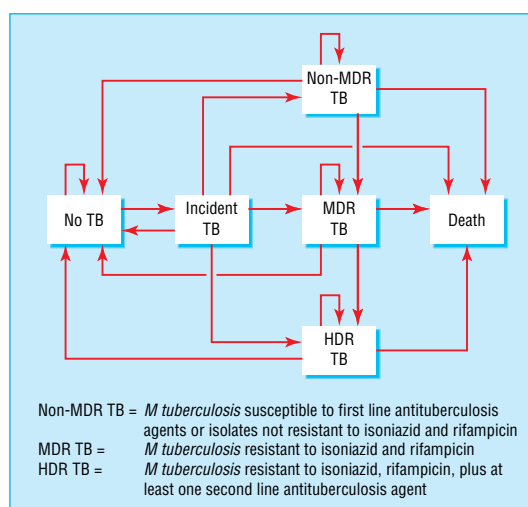
### In addition:

- Mycobacterial cultures and drug susceptibility testing are not required
- Treatment is started on the basis of symptoms or a positive smear
- Second line drugs are not used
- Three categories of treatment regimens exist; all are directly observed
- In the developing world, mycobacterial cultures and susceptibility testing are generally not performed, so drug resistance is not detected even if it is present

### In DOTS-plus:

- Second line antituberculosis drugs (more toxic and expensive, and less effective, than first line drugs) are used. The regimen includes two or more drugs to which the isolate is susceptible, including one drug given parenterally for six months or more. Total duration of treatment 18-24 months; treatment is directly observed
- Treatment regimen is either:  
Individualised according to drug susceptibility test results of the *M tuberculosis* isolate identified on culture; or  
Given as a standardised regimen to patients who fail supervised retreatment (for example, when culture and drug susceptibility testing are not performed).
- Mycobacterial cultures and drug susceptibility testing may be performed.

rates. When we assessed DOTS-plus for decreased levels of effectiveness of the programme, survival and cure rates of multidrug resistant, highly drug resistant, and non-multidrug resistant tuberculosis fell by a percentage of the baseline rate (for example, 5%), and the rate of patients developing highly drug resistant tuberculosis rose.



Transition states of the Markov analysis

Cumulative number of deaths (due to prevalent cases of tuberculosis at the start of the analysis and to incident cases during the 10 year period under analysis) from tuberculosis per 100 000 population during a 10 year period. Decrements in effectiveness of treatment are compared with baseline DOTS. Numbers in parentheses represent the increase or decrease (–) in the cumulative number of deaths compared with DOTS

Control programme*	Resistance level of <i>Mycobacterium tuberculosis</i>			Total
	Non-multidrug resistant	Multidrug resistant	Highly drug resistant	
<b>3% incident tuberculosis</b>				
DOTS	252	24	0	276
DOTS-plus:				
Optimal implementation	256 (4)	16 (–8)	0	272 (–4)
5% decrease in effectiveness of DOTS	292 (40)	20 (–4)	8 (8)	320 (+44)
10% decrease in effectiveness of DOTS	388 (136)	28 (4)	4 (4)	420 (+144)
<b>10% incident tuberculosis</b>				
DOTS	212	108	0	320
DOTS-plus:				
Optimal implementation	216 (4)	68 (–40)	4 (4)	288 (–32)
5% decrease in effectiveness of DOTS	256 (44)	100 (–8)	16 (16)	372 (+52)
10% decrease in effectiveness of DOTS	316 (104)	120 (12)	12 (12)	448 (+128)

### Cost effectiveness

In the example used for this analysis, we used marginal cost estimates from India. For DOTS, the marginal cost per patient was \$10 (£6; €10) (T R Frieden, unpublished data, 2000).<sup>9</sup> For DOTS-plus, we assumed that no more than 10% of patients would receive second line drugs and culture and susceptibility testing. The average cost per patient under DOTS-plus would be approximately \$230 and the marginal added cost of DOTS-plus (compared with DOTS) would be \$230 – \$10=\$220 (see [bmj.com](http://bmj.com) for details.)

## Results

### Optimal implementation of DOTS

Based on the probabilities for a hypothetical cohort treated with DOTS and for a setting in which the proportion of primary multidrug resistant tuberculosis is 3%, 276 deaths per 100 000 population would occur during a 10 year period among smear positive cases of pulmonary tuberculosis. Of these, 252 would have non-multidrug resistant and 24 multidrug resistant disease (table).

### Optimal implementation of DOTS-plus

Four (1.5%) fewer patients would die with tuberculosis under optimal implementation of DOTS-plus than under DOTS. Eight fewer patients would die with multidrug resistant tuberculosis, but four more would die with non-multidrug resistant tuberculosis (table).

### Suboptimal implementation of DOTS-plus

Since DOTS-plus may not be implemented optimally and its effectiveness would therefore be diminished, we performed the analysis for scenarios in which the survival and cure rates of patients with non-multidrug resistant and multidrug resistant tuberculosis were each 5% or 10% less effective than in the DOTS analysis. In addition, the risk of developing highly drug resistant tuberculosis increased with decreasing effectiveness of the programme. If attention to DOTS-plus were to divert resources from DOTS and result in tuberculosis survival and cure rates just 5% less than those under DOTS, 44 more patients would die with tuberculosis than under DOTS, which represents a 16% increase in the number of deaths. If DOTS-plus were 10% less effective than optimal DOTS, 144 addi-

tional patients would die compared with DOTS, which represents a 52% increase (table).

### DOTS and DOTS-plus in “hotspots” of multidrug resistant tuberculosis

We then compared the effectiveness of DOTS and DOTS-plus in an area where a high proportion (10%) of cases of incident tuberculosis had multidrug resistance and also adjusted the prevalence of multidrug resistant and non-multidrug resistant tuberculosis. Under optimal conditions, DOTS-plus would result in 40 fewer deaths from multidrug resistant tuberculosis than DOTS but also four deaths from highly drug resistant tuberculosis that would not have occurred under DOTS. Overall, optimal DOTS-plus would result in 10% fewer deaths than DOTS. If DOTS-plus were to divert resources from DOTS such that DOTS was just 5% less effective than under optimal conditions, however, 52 more patients would die from tuberculosis than under baseline DOTS, representing a 16% increase in the number of deaths (see table). If the effectiveness of the control programme decreased by 10%, 128 more patients would die with tuberculosis than under DOTS, representing a 40% increase.

### Incremental cost effectiveness of DOTS-plus

In a setting in which the proportion of primary multidrug resistant tuberculosis is 3%, the number needed to treat under DOTS-plus to avert one death compared with treating all patients under DOTS would be  $1/(276 - 272)/1250=313$  patients, where the denominator of 1250 represents prevalent and incident cases per 100 000 population with initial treatment over 10 years. Assuming a marginal added cost of DOTS-plus of \$220, the incremental cost effectiveness ratio would be  $\$220 \times 313 = \$68\,860$  spent for each death averted. In a setting where the proportion of primary multidrug resistant tuberculosis is 10%, the number needed to treat under DOTS-plus would be  $1/(320 - 288)/1250=39$  patients, with an incremental cost effectiveness ratio of  $\$220 \times 39 = \$8580$ .

## Discussion

### Limitations of the study

This study has several limitations. Firstly, we did not include morbidity due to adverse reactions to the

drugs in the analysis. Given the greater toxicity of the second line antituberculosis agents used for DOTS-plus, this would be yet another caution against widespread use of the strategy. Secondly, although the model incorporated the risk of reinfection with *M tuberculosis*, it did not measure the impact of secondary transmission from people with active tuberculosis. This would tend to underestimate both the potential benefits of DOTS and the potential negative impact of poor implementation. Thirdly, we assumed that highly drug resistant tuberculosis could not develop in settings where second line drugs were not used in the treatment regimen. This may not be true in areas where agents such as fluoroquinolones are widely available. However, the risk of developing highly drug resistant tuberculosis in such settings has not been measured and was therefore not included in the analysis. HIV was not accounted for in the analysis because of insufficient data on the effectiveness of DOTS and DOTS-plus among HIV positive patients. Although HIV infection is associated with an increased risk of tuberculosis among patients infected with *M tuberculosis*, it is not associated with an increased rate of drug resistant tuberculosis.<sup>10</sup>

### Strengths of the study

Although our baseline analysis assumed that DOTS-plus can be implemented effectively, the proportion of patients completing even standard treatment regimens is low in areas where multidrug resistant tuberculosis has become a major problem.<sup>11</sup> In areas where direct smear microscopy and giving two to four relatively non-toxic drugs for six months is impossible, routinely performing mycobacterial cultures and first and second line susceptibility testing as well as administering four to seven toxic drugs for 18-24 months is unlikely to be possible.

A tuberculosis control programme should have implemented effective DOTS before implementing DOTS-plus.<sup>12</sup> A poorly run control programme can generate multidrug resistant tuberculosis, but effective DOTS can decrease the rates of multidrug resistant tuberculosis.<sup>13</sup> More widespread implementation of effective DOTS would therefore decrease the number of cases for which DOTS-plus would be necessary.<sup>14</sup> Currently, 77% of tuberculosis cases worldwide are not treated even with DOTS.<sup>15</sup>

The incremental cost effectiveness ratio in our baseline model for DOTS-plus (\$68 860 to avert one death under DOTS-plus compared with DOTS) is within range of other treatments. However, when the implementation of DOTS-plus leads to reduced effectiveness of DOTS, the DOTS-plus strategy is both less effective and more costly. Given the variation in costs per patient, fixed programme costs, and drug resistance among different geographical regions, as well as population size, further modelling would be necessary to make a recommendation for a local jurisdiction.

This analysis does not indicate that DOTS-plus should not be implemented. Rather, it shows the very notable risks associated with implementation of DOTS-plus and shows that, where the strategy is implemented, second line drugs must be used effectively and first line treatment strengthened and insulated from the demands of providing second line drugs on a programme basis.

### What is already known on this topic

DOTS is an effective, albeit underused, strategy for treating tuberculosis

DOTS may be insufficiently effective in treating multidrug resistant tuberculosis

The use of toxic reserve drugs (DOTS-plus) is an effective but costly strategy for treating multidrug resistant tuberculosis

The impact of the implementation of DOTS-plus on overall tuberculosis control is unknown

### What this study adds

If implementation of DOTS-plus is associated with even minimal decreases in the effectiveness of DOTS, more patients would die from tuberculosis under DOTS-plus than under DOTS alone

If DOTS-plus is implemented, it must not divert resources from and decrease the effectiveness of DOTS

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- 1 World Health Organization. *Treatment of tuberculosis. Guidelines for national programmes. WHO report.* Geneva: WHO, 1997. (WHO/CDS/TB/97.220.)
- 2 Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986;133:423-30.
- 3 Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis. Treatment outcomes in 6 countries. *JAMA* 2000;283:2537-45.
- 4 Farmer P, Kim JY. Community based approaches to the control of multidrug resistant tuberculosis: introducing "DOTS-plus." *BMJ* 1998;317:671-4.
- 5 Telzak EE, Sepkowitz K, Alpert P, Mannheimer S, Medard F, El-Sadr W, et al. Multidrug-resistant tuberculosis in patients without HIV infection. *N Engl J Med* 1995;333:907-11.
- 6 Tahaoglu K, Torun T, Sevim T, Atac G, Kir A, Karasulu L, et al. The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med* 2001;345:170-4.
- 7 Espinal MA, Dye C, Raviglione M, Kochi A. Rational "DOTS plus" for the control of MDR-TB. *Int J Tuberc Lung Dis* 1999;3:561-3.
- 8 Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making* 1983;3:419-58.
- 9 World Health Organization. *Joint tuberculosis programme review, India.* Geneva: WHO; February 2000. (WHO Project No ICP TUB030.)
- 10 Spellman CW, Matty KJ, Weis SE. A survey of drug-resistant Mycobacterium tuberculosis and its relationship to HIV infection. *AIDS* 1998;12:191-5.
- 11 Pablos-Mendez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al. Global surveillance for antituberculosis-drug resistance, 1994-1997. *N Engl J Med* 1998;338:1641-9.
- 12 Lambregts-van Weezenbeek KSB, Reichman LB. DOTS and DOTS-Plus: what's in a name. *Int J Tuberc Lung Dis* 2000;4:995-6.
- 13 Ledru S, Cauchois B, Yameogo M, Zoubga A, Lamande-Chiron J, Portals F, et al. Impact of short-course therapy on tuberculosis drug resistance in south-west Burkina Faso. *Tuberc Lung Dis* 1996;77:429-36.
- 14 Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: strategies to beat multidrug-resistant tuberculosis. *Science* 2002;295:2042-6.
- 15 World Health Organization. *Global tuberculosis control: WHO report.* Geneva: WHO, 2001. (WHO/CDS/TB/2001.287.)

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