Impact of DOTS compared with DOTS-plus on multidrug resistant tuberculosis and tuberculosis deaths: decision analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
This study investigated the treatment of tuberculosis (TB) with the directly observed treatment, short course (DOTS) and DOTS-plus treatment strategies. DOTS is a World Health Organization programme that requires governments to administer a national TB programme, with detection of cases through case-finding by smear microscopy examination of susceptible patients. Smear-positive patients are treated using standardised short-course chemotherapy with the first-line drugs isoniazid, rifampicin, pyrazinamide and ethambutol. The programme also requires a regular uninterrupted supply of drugs and a system for monitoring and evaluation. DOTS-plus comprises the DOTS programme plus second-line treatment with two or more anti-tuberculosis drugs to which the isolate is susceptible for 18 to 24 months.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised human immunodeficiency virus (HIV)-negative adults with smear-positive pulmonary TB in the developing world.

Setting
The setting was unclear, but it was likely to have been primary and secondary care. The economic study was carried out in the USA.

Dates to which data relate
The estimates of effectiveness were derived from studies published between 1934 and 2002. The dates to which the resource use related were not reported. The price year was unclear, but it was likely to have been 2001.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies and authors' assumptions.

Modelling
A Markov model was used to estimate the impact of the two programmes over a 10-year period. A cycle length of 1 year was used. A Monte Carlo simulation of 25,000 iterations was performed to express the cumulative health benefit as the rate per 100,000 people during the 10-year period. DOTS and DOTS-plus were analysed for differing levels of programme effectiveness, under conditions with moderate (3%) and high (10%) proportions of cases of incident multidrug-resistant TB.
Outcomes assessed in the review
The following model input parameters were derived from published primary studies:

- the proportion of incident TB that is multidrug resistant;
- the annual incidence of TB;
- the prevalence of multidrug-resistant TB;
- the prevalence of non multidrug-resistant TB;
- the percentage of patients with TB who were treated;
- the percentage of patients who were alive, and the percentage of patients who were cured for multidrug-resistant and non multidrug-resistant TB;
- the percentage of patients who were alive and the percentage of patients who were cured if TB was not treated; and
- the percentage of patients with prevalence multidrug-resistant and non multidrug-resistant TB following treatment and no treatment.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
MEDLINE and global reports published by the World Health Organization were searched for primary studies and relevant data.

Criteria used to ensure the validity of primary studies
Peer-reviewed articles and World Health Organization reports were included in the review. Whenever possible, studies conducted in the developing world were used. Studies evaluating the effectiveness of DOTS-plus that included surgical management were excluded to maintain comparability with studies evaluating the effectiveness of DOTS.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The model input parameters were identified from 13 studies.

Methods of combining primary studies
Where more than one estimate of a model parameter was found, the mean value was used.

Investigation of differences between primary studies
Not reported.

Results of the review
The following model input parameters were derived from published primary studies:
3% (10% under second condition) of incident TB is multidrug resistant;

the annual incidence of TB was 100 per 100,000 population;

the prevalence of multidrug-resistant TB was 25 per 100,000 population (100 per 100,000);

the prevalence of non multidrug-resistant TB was 225 per 100,000 population (150 per 100,000);

70% of patients with TB were treated;

91% of patients were alive following treatment for multidrug-resistant TB under DOTS, compared with 94% of those treated under DOTS-plus;

96% of patients were alive following treatment for non multidrug-resistant TB under DOTS and DOTS-plus; and

50% of patients were alive if not treated under DOTS and DOTS-plus.

**Methods used to derive estimates of effectiveness**
Authors’ assumptions were used to obtain some of the estimates of effectiveness.

**Estimates of effectiveness and key assumptions**
Patients with prevalence multidrug-resistant TB had a lower chance of cure without specific treatment than other untreated patients (e.g. 10% versus 20%);

Patients with highly drug-resistant TB treated with DOTS-plus were less likely to be cured and to survive than patients with multidrug-resistant TB treated with DOTS-plus.

Patient treated under DOTS-plus received second-line agents and could, therefore, develop resistance to these drugs, whereas patients treated under DOTS were assumed not to.

**Measure of benefits used in the economic analysis**
The measure of health benefit used was the number of TB deaths averted. This information was taken from the model (described above).

**Direct costs**
This economic analysis assessed the marginal costs of the health care provider. The paper did not provide a breakdown of the individual costs included in the estimates of total marginal costs. However, it did report that the costs of medicine, medical personnel and laboratory costs were included. No breakdown of the resource use and unit costs was provided. Estimates of resource use and costs were taken from published studies. Marginal cost estimates from India were used. No price year was reported. The paper did not indicate whether the future costs were discounted.

**Statistical analysis of costs**
No statistical analysis of the costs was undertaken.

**Indirect Costs**
No indirect costs were included in this analysis.

**Currency**
US dollars ($).
**Sensitivity analysis**
A sensitivity analysis that considered the impact of variability of the clinical data was undertaken. It appears to have been a one-way analysis. The ranges of the variables were taken as plus and minus 10% of the baseline value.

**Estimated benefits used in the economic analysis**
Given a 3% incident rate of TB implementation of the DOTS programme, a total of 276 deaths per 100,000 population would occur over 10 years.

Assuming optimum implementation of the DOTS-plus programme, a total of 272 deaths per 100,000 population would occur over 10 years. However, if the implementation of the DOTS-plus programme was 5% (or 10%) less effective than in the DOTS analysis, 320 (or 420) deaths per 100,000 population would occur over 10 years.

Given a 10% incident rate of TB, the DOTS programme would result in 320 deaths per 100,000 population over 10 years.

Assuming optimum implementation of the DOTS-plus programme, 288 deaths would occur per 100,000 population over 10 years. However, if the implementation of the DOTS-plus programme were 5% (or 10%) less effective than in the DOTS analysis, 372 (or 448) deaths per 100,000 population would occur over 10 years.

**Cost results**
The marginal costs per patient were $10 under the DOTS programme and $220 under the DOTS-plus programme.

**Synthesis of costs and benefits**
Assuming a 3% incident rate of TB, the incremental cost-effectiveness ratio (ICER) of the DOTS-plus programme compared with the DOTS programme was $68,860 per death averted.

If a 10% incident rate of TB was assumed, the ICER of the DOTS-plus programme compared with the DOTS programme was $8,580 per death averted.

The sensitivity analysis indicated that alterations in the input variables did not alter the rank order of the two programmes.

**Authors' conclusions**
Under optimum implementation, fewer tuberculosis (TB) deaths occur under the DOTS (directly observed treatment, short course)-plus programme than under the DOTS programme and the incremental cost-effectiveness ratio (ICER) for DOTS-plus is within the range of other treatments. However, if the DOTS-plus programme is associated with even minimal decreases in the effectiveness of treatment, DOTS-plus is both less effective and more costly.

**CRD COMMENTARY - Selection of comparators**
DOTS was chosen as the comparator because it is the World Health Organization's recommended strategy for the treatment of smear pulmonary TB. You should consider how this relates to current practice in your setting prior to applying the results of this study.

**Validity of estimate of measure of effectiveness**
The clinical effectiveness data used in this analysis were modelled. The model input parameters were taken from a review of primary studies. The authors did not state whether or not they undertook a systematic review, although they did report the sources searched and some selection criteria. Where the review identified more than one estimate of an input parameter, the authors took the mean value; this was appropriate. However, the authors did not comment on
possible reasons for differences between the primary studies. The authors made several assumptions about effectiveness, but these estimates were investigated in a sensitivity analysis.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The instrument used to derive a measure of health benefit (i.e. the Markov model) was appropriate. No justification for the choice of measure (i.e. number of TB deaths) was given. The use of alternative measures that include quality of life (e.g. the number of quality-adjusted life-years gained) would have been useful for comparing the results of this study with those of different interventions. Although benefits could be incurred over a 10-year period, the future benefits do not appear to have been discounted.

**Validity of estimate of costs**
The paper did not report the economic perspective of the analysis. However, the study appears to have adopted the perspective of a health care provider. The paper did not provide a breakdown of the resource use or unit costs. This information was taken directly from published studies and was treated deterministically. These facts make it difficult to apply the results of the study to other settings and to establish whether all the appropriate costs were included. Variability in the cost data does not appear to have been assessed and no price year was reported; these facts limit the generalisability of the study findings and prevent any future reflation exercises. The paper did not indicate whether the future costs were discounted to take account of the preference for current benefit.

**Other issues**
The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. They did not compare their findings with those from other studies in the same area. Nor did they consider how their results may be generalised to other patient populations or other settings.

The authors reported a number of further limitations. First, mortality due to adverse reactions to drugs was not taken into consideration. The greater toxicity of the second-line anti-tuberculosis agents used for DOTS-plus would be another disadvantage of the widespread use of the strategy. Second, secondary transmission of TB from people with active TB was also not considered. This would tend to underestimate both the potential benefits of DOTS and the potential negative impact of poor implementation. Finally, the authors also assumed that highly drug-resistant TB would not be present in areas where the DOTS-plus programme was not used.

**Implications of the study**
The authors suggested that, 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 before making a recommendation for a local jurisdiction.

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