Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection
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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.

CRD summary
The objective was to assess the cost-effectiveness of alternative treatments for latent tuberculosis infection. The authors concluded that rifampin was cost-saving compared with self-administered isoniazid and isoniazid plus rifapentine was cost-saving for extremely high-risk patients and was cost-effective for lower risk patients. While the analysis was reasonably well conducted, the authors' conclusions do not appear to adequately account for the uncertainty in the treatment effectiveness estimates.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The objective was to assess the cost-effectiveness of treatments for latent tuberculosis infection (LTBI), which was defined as a newly positive tuberculin skin test after recent exposure to infectious tuberculosis.

Interventions
The four treatment regimens were: self-administered isoniazid daily for nine months (the standard treatment); directly observed isoniazid twice-weekly for nine months; directly observed isoniazid plus rifapentine once weekly for three months; and self-administered rifampin daily for four months. No intervention was also included as a comparator.

Location/setting
USA/community and primary care.

Methods
Analytical approach:
A Markov model analysed a hypothetical cohort of adults, with LTBI and an average age of 39 years, over their lifetimes. The health states included: on treatment, off treatment, active TB, post TB, and dead due or not due to TB infection. Patients who developed active TB were at risk of death from it during the period of treatment. After treatment was completed, patients were considered to be cured and moved to the post-TB state. No patient was assumed to have TB more than once. The authors stated that a societal perspective was adopted.

Effectiveness data:
The estimates of efficacy, defined as the reduction in risk of TB, were from a published study of self-administered and directly observed isoniazid treatment; the International Union against Tuberculosis Committee on Prophylaxis (IUAT) trial (1982, see ‘Other Publications of Related Interest’ below for bibliographic details). Assumptions and interpolations were made for the efficacy of the isoniazid plus rifapentine and of rifampin. Protection was assumed to remain for the lifetime with all treatments. The authors used their judgement to select the most appropriate estimates from the literature for extended treatment for active disease, death from TB, secondary cases per active TB cases, treatment adherence, and treatment-related adverse events (resulting in withdrawal, hospitalisation, or death). The treatment adherence was mainly from studies in high-risk populations who were given the directly observed isoniazid treatment. The TB-related and all-cause age-specific mortality estimates were from US populations. A few authors’ assumptions were necessary and these were reported in detail in an online data supplement.

Monetary benefit and utility valuations:
The utilities were assigned for five conditions: LTBI treatment, treatment-limiting toxicity, hospitalisation, treatment
of active TB, and prior TB. The utility values were from two published sources; Guo, et al. 2008 (see 'Other Publications of Related Interest' below for bibliographic details) for LTBI treatment, and the State of North Carolina Tuberculosis Control Program. 2007 (see 'Other Publications of Related Interest' below for bibliographic details) for treatment of active TB. Authors' assumptions were made for the other conditions.

Measure of benefit:
Quality-adjusted life-years (QALYs) and the number of active tuberculosis cases prevented were the summary benefit measures. Health outcomes were discounted at 3% per annum.

Cost data:
The direct costs of the treatment of LTBI, per month, included nursing, physician and outreach worker visits, monitoring, laboratory tests and hospitalisation for toxicity, medications, travel, and patient time. The direct costs for active TB treatment included diagnosis, in-patient and out-patient care, patient time, and contact tracing and testing. The costs and resource use for the treatment of LTBI were from a variety of published sources, and personal communications (drug costs). Those for active TB treatment were predominantly from one US study (Burman, et al. 1997, see 'Other Publications of Related Interest' below for bibliographic details). All costs were in US dollars ($) and were discounted at an annual rate of 3%. The price year was 2008.

Analysis of uncertainty:
One-way sensitivity analysis was performed on a wide range of model parameters including: the completion rates, treatment efficacies, probability of developing active TB (for various populations at high risk, such as those with diabetes mellitus or human immunodeficiency virus (HIV) infection), toxicity rates, utilities, and costs. The authors used a cost-effectiveness threshold of $50,000 per QALY according to the recommendations of the Panel on Cost-effectiveness in Health and Medicine.

Results
The average lifetime cost per contact, with a lifetime risk of TB of 0.06, was: $1,527.33 for no intervention, $679.52 for self-administered daily isoniazid, $2,002.42 for directly observed isoniazid, $495.21 for rifampin, and $776.27 for isoniazid plus rifapentine.

The number of QALYs was 22.671 with isoniazid plus rifapentine, 22.665 with rifampin, 22.656 with directly observed isoniazid, 22.645 with self-administered isoniazid, and 22.596 with no intervention. Rifampin dominated all other regimens, as it was more effective and less costly, except isoniazid plus rifapentine, which was more effective, but more expensive with a cost per QALY gained of $48,997.

Doubling the baseline lifetime risk of disease activation resulted in a cost per QALY for isoniazid plus rifapentine of $20,099; at 5.2 times the relative risk, the costs for isoniazid plus rifapentine and for rifampin were equivalent, but isoniazid plus rifapentine was more effective; at 10 times the relative risk rifapmin dominated all other regimens. Isoniazid plus rifapentine was dominant when there was low adherence to both of the self-administered treatments (isoniazid, 34% and rifampin 37%). Rifampin was still the dominant treatment when its efficacy was up to 17% less than that of self-administered isoniazid.

The results were insensitive to variations in the utility scores, toxicity, and costs of the treatment of active disease.

Authors’ conclusions
The authors concluded that rifampin was cost-saving over the patient’s lifetime compared with the standard therapy of self-administered isoniazid. Isoniazid plus rifapentine was the most effective treatment; it was cost-saving for extremely high-risk patients (5.2 times based case risk of disease) and cost-effective for lower risk patients (base case risk 0.06) at the threshold of $50,000 per QALY.

CRD commentary
Interventions:
The selection of the comparators was appropriate as the available strategies for the treatment of LTBI were examined, including the usual policy implemented in the US setting at the time.
Effectiveness/benefits:
The clinical trials that provided the treatment effectiveness for three of the regimens were the only available trials and the effectiveness for isoniazid plus rifapentine was mainly based on authors assumptions and interpolations. Detailed information on the other sources of data was not provided, which makes it impossible to objectively judge the internal validity of the clinical data, but this issue was extensively investigated in the sensitivity analyses. QALYs were appropriate as the key benefit measure, but the authors did not explicitly state the method that they used to measure the utilities.

Costs:
The included resource use and cost estimates were representative of the societal perspective. The unit costs and resource use were reported separately and they were from published US sources. The authors cited personal communication as the source for medication costs, but it was not clear if these were published market prices. Variations in the cost estimates were considered in the sensitivity analysis. Other details of the analysis, such as the data sources, price year, and discounting, were reported.

Analysis and results:
The costs and benefits were appropriately analysed, using an incremental approach. The analysis considered patient populations with different risks of activation thus ensuring that the findings were relevant to different groups of individuals. The issue of uncertainty was satisfactorily addressed by performing extensive one-way sensitivity analyses on the key model parameters. The authors acknowledged that a major limitation of their study was the lack of data for deriving the estimates of efficacy and adherence for isoniazid plus rifapentine and that their results needed to be confirmed, using the findings of a large multicentre trial of high-risk patients with LTBI, when available (clinicaltrials.gov, see 'Other Publications of Related Interest' below for the reference).

Concluding remarks:
While the analysis was reasonably well conducted, the authors’ conclusions do not appear to adequately account for the uncertainty in the treatment effectiveness estimates.

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