Potential cost-effectiveness of rifampin vs. isoniazid for latent tuberculosis: implications for future clinical trials

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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 study assessed the cost-effectiveness of four months of rifampin compared with nine months of isoniazid treatment for latent tuberculosis. The authors concluded that rifampin may be a reasonable alternative to isoniazid, but that definitive results would require large-scale efficacy trials. The overall quality of the study methods and reporting were adequate. Given the hypothetical scope of the study, the authors’ conclusions appear to be valid.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The objective of the study was to identify the efficacy threshold that would make rifampin cost-effective compared with isoniazid for latent tuberculosis (participants with tuberculosis clinics with positive tuberculosis skin tests).

Interventions
A four-month daily rifampin regime was compared with a nine-month daily isoniazid regime (standard treatment). The two interventions were also compared with no treatment.

Location/setting
Canada/outpatient secondary care.

Methods
Analytical approach:
A Markov model used time-dependent probabilities of tuberculosis risks and adverse events from a single clinical trial (Menzies, et al. 2008, see 'Other Publications of Related Interest' for bibliographic details). The time horizon was 20 years. The perspective adopted was not reported.

Effectiveness data:
Grade 3 or 4 side effects and completion rates came from one multicentre randomised clinical trial (Menzies, et al. 2008) conducted in Canada, Brazil and Saudi Arabia. In the trial, which included data for side effects and completion rates, participants were recruited from nine tuberculosis clinics; 420 were randomised to the rifampin group and 427 were randomised to the isoniazid group. Completion rates were defined as taking 80% or more of prescribed medications.

Efficacy rates and the prevention of subsequent active tuberculosis did not come from this trial. For the isoniazid group, the efficacy rate came from another trial. For rifampin groups (the base case), an efficacy rate was assumed which was the lower level of efficacy that would be accepted in a non-inferiority trial. The efficacy rate was varied to identify the threshold at which four months of rifampin became cost-effective.

Monetary benefit and utility valuations:
Not relevant.

Measure of benefit:
The measure of benefit was the number of active tuberculosis cases per 1,000 patients. As benefits could be generated
over a 20-year time horizon, future benefits were discounted using an annual rate of 3%.

Cost data:
The direct costs included were physician fees, nursing care, laboratory tests, consultations with other services, pharmacy fees, prescription drugs, and treatment of active tuberculosis. Health system resource use, except those of treating active tuberculosis cases, was taken from the clinical trial that compared four months of rifampin with nine months of isoniazid and valued using fees from the province of Quebec. Costs for active tuberculosis cases were obtained from the Public Health Agency of Canada. Indirect costs were lost productivity with absence from work due to scheduled and non-scheduled healthcare visits by the participants. Absence from work was valued using Canadian minimum hourly wages. Costs were reported in Canadian dollars (CAD). As costs could be incurred over a 20-year time horizon, future costs were discounted using an annual rate of 3%. The price year was 2007.

Analysis of uncertainty:
One-way sensitivity analyses were undertaken by varying model parameters over a range of plausible values. In particular, due to the lack of evidence for the efficacy of four months of rifampin, its efficacy was varied from 60% to 95%. Two-way sensitivity analyses were performed for several key parameters.

Results
The number of active tuberculosis cases expected per 1,000 patients was 54 with no treatment and 29 with nine months of isoniazid treatment. For four months of rifampin, the number of active tuberculosis cases per 1,000 patients was 29 assuming 60% efficacy, and 14 cases at 95% efficacy.

The cost per 1,000 patients was CAD 1,461,990 for no treatment and CAD 1,730,260 for nine months of isoniazid treatment. For four months of rifampin, the cost per 1,000 patients was CAD 1,703,010 assuming 60% efficacy, and CAD 1,305,130 at 95% efficacy.

Costs and benefits were combined using an incremental cost-effectiveness ratio (the additional cost per active tuberculosis case prevented). For 60% efficacy, nine months of isoniazid had extended dominance over four months of rifampin. For 65% efficacy, the incremental cost-effectiveness ratio (ICER) of four months of rifampin compared with no treatment was CAD 6,697, and the ICER of nine months of isoniazid was CAD 53,739 compared with rifampin. For 70% efficacy or above, four months of rifampin was dominant over nine months of isoniazid (as it was more effective and less costly). For 85% efficacy or more, rifampin became dominant over no treatment.

The authors reported that, regardless of the cost of treatment of active tuberculosis, four months of rifampin became cheaper and more effective than nine months of isoniazid once its efficacy exceeded 69%.

Authors’ conclusions
The authors concluded that rifampin may be a reasonable alternative to isoniazid, but that definitive results would require large-scale efficacy trials.

CRD commentary
Interventions:
The interventions studied were reported in detail.

Effectiveness/benefits:
Clinical and effectiveness data came from previously published studies; most of the data was from a multicentre randomised controlled trial. Data on drug completion rates and complication rates came from this trial. However, due to the small sample size and lack of long-term follow-up, the trial did not provide any efficacy estimate for treatment with four months of rifampin. So the authors conducted a series of scenario analyses assuming variation in efficacy of four months of rifampin from 60% to 95%. The authors acknowledged the lack of efficacy estimates for four months of rifampin treatment in the published literature.

Costs:
The perspective adopted in the economic analysis was not explicitly reported by the authors. However, it would appear that a societal perspective was adopted as the authors included both direct and indirect costs. All major relevant
healthcare costs appear to have been included in the analysis. The authors adequately reported the sources for the included costs. The price year, time horizon, discount rate used and currency details were adequately reported.

**Analysis and results:**
Costs and outcomes were combined using a decision-tree Markov model. Appropriate details of the model structure were provided including a diagram. One-way sensitivity analyses were undertaken. Although this type of analysis went some way to evaluate uncertainty, the use of a probabilistic sensitivity analysis would have been a better way to evaluate overall uncertainty. As main limitation to their study, the authors acknowledged that their analysis involved some simplifying assumptions and that they did not consider patients infected with HIV.

**Concluding remarks:**
The overall quality of the study methods and reporting were adequate and appropriate. Given the hypothetical scope of the study, the authors' conclusions appear to be valid.

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