Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a cost-effectiveness analysis based on a multicenter clinical trial

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
Two months' treatment with rifampin and pyrazinamide (R-Z) was compared with 6 months of isoniazid (IS) for the treatment of latent tuberculosis (TB) infection in adults without human immunodeficiency virus (HIV) infection.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adults aged 17 years or older with a positive tuberculin skin test result (defined by ATS/CDC criteria), in whom active TB was excluded, and in whom treatment of latent TB infection would ordinarily be recommended (e.g. close contact with an infectious case, or medical risk factor such as diabetes). The exclusion criteria included pregnancy, HIV infection and a history of gout. Further exclusion criteria were a serum creatinine level of more than twice the upper limit of normal, and a serum aspartate aminotransferase or alanine aminotransferase level of more than 1.5 times the upper limit of normal.

Setting
Although not explicitly stated, the setting was likely to have been secondary care (outpatient setting). The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence was based mainly on the results of a multi-centre, prospective open-label trial, conducted by the same authors and published in 2002, and additional studies published between 1970 and 2001. The resource use estimates were derived from data reported in studies published in 2001-2002. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies and authors' assumption. The majority of the data were derived from a sample of patients participating in a clinical trial (Jasmer et al., see 'Other Publications of Related Interest' for bibliographic details).

Study sample
Patients who met the study criteria and who agreed to participate were allocated to either R-Z or IS. Data used in the present study were derived from 350 patients who were enrolled at one of the study sites (San Francisco). Of these, 184 received R-Z and 166 received IS. Further details were provided in the parent publication (Jasmer et al., see 'Other
Publications of Related Interest’ for bibliographic details). No power calculations were reported.

**Study design**
The study was a multi-centre, prospective open-label trial that was conducted in three sites (San Francisco, Boston and Atlanta). Data from the 350 patients enrolled in San Francisco were used in the present study. The duration of follow-up appears to have been 2 months in the R-Z group and 6 months in the IS group. No loss to follow-up was reported.

**Analysis of effectiveness**
It was not stated whether the analysis was conducted on an intention to treat basis or on treatment completers only. The primary health outcomes assessed included the development of any adverse events and the completion rate of the prescribed amount of treatment. Completion was defined as taking 80% or more of the prescribed medication. It was stated that the two groups were similar in terms of gender, weight and indication for treatment of latent TB infection.

**Effectiveness results**
More patients in the R-Z group experienced Grade 3 or 4 hepatotoxicity than in the IS group (12 versus 1; p=0.004). Of these, 9 in the R-Z group and 1 in the IS group discontinued therapy as a result, (p=0.02).

There was no significant difference in the overall rate of other adverse effects between the two groups, (p=0.70). However, skin rash was seen more frequently in patients who received R-Z, (p=0.02).

The percentage of patients who completed treatment was similar between the groups, 66% of the R-Z group and 68% of the IS group, (p=0.67).

**Clinical conclusions**
R-Z was associated with a higher rate of hepatotoxicity than IS, although the rates of other adverse events resulting from treatment were similar for both regimens. Completion of treatment was also similar between the two interventions.

**Modelling**
A Markov model was developed to evaluate the cost-effectiveness of the two interventions examined. A hypothetical cohort of 1,000 patients aged 35 years, with latent TB infection, received either R-Z daily for 2 months, IS daily for 6 months, or no treatment. The cohort was followed up until the age of 99 years (or death). Expected completion rates of treatment, adverse events and costs were determined on the basis of data derived from a parent study. Three key assumptions were used in the model. First, each patient was at risk of developing active TB, dying from TB, or dying from other causes. Second, no patients were resistant to IS, although the rate of IS-resistant infection was varied in the sensitivity analysis. Third, no deaths occurred in association with R-Z treatment.

**Outcomes assessed in the review**
The outcomes assessed included:

the efficacy of R-Z and IS for various durations of therapy, expressed as a reduction in the risk of TB;

the annual risk of TB when no treatment of latent infection was applied;

the age-specific risk of death due to TB; and

the annual, all-cause risk of death.

**Study designs and other criteria for inclusion in the review**
The annual risk of TB was derived from a general review. The efficacy of treatment of latent TB infection was derived from a clinical trial. The age-specific risks of death were derived from a published cost-effectiveness analysis.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

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

**Number of primary studies included**
Two primary studies and one review were included in the review.

**Methods of combining primary studies**
The results of the primary studies were not combined since their primary outcomes were different.

**Investigation of differences between primary studies**
Not relevant since the studies included in the review evaluated different primary outcomes.

**Results of the review**
The reduction in risk of TB was:

- 69% after 2 months of R-Z therapy or 6 months of IS therapy;
- 20% after 1 month of R-Z therapy or 3 to 5 months of IS therapy; and
- 0% after less than 1 month of R-Z therapy or less than 3 months of IS therapy.

The annual risk of TB without treatment of latent infection was 0.27.

The relative risk of death due to TB was 3.9 for patients aged 35 - 44 years old, 7.4 for patients aged 45 - 64 years old, and 16.8 for patients aged 65 years or older.

The annual, age-specific all-cause risk of death was not reported.

**Methods used to derive estimates of effectiveness**
The study was also based on authors' assumptions.

**Estimates of effectiveness and key assumptions**
Since there were no studies evaluating the efficacy of R-Z therapy in adults without HIV infection, it was assumed that its efficacy was equal to that of IS administered to patients without HIV infection.

**Measure of benefits used in the economic analysis**
The outcomes of the analysis were the number of TB cases averted, the number of TB-related deaths avoided, and the...
difference in life expectancy between each cohort. The health benefits were discounted at an annual rate of 3%.

**Direct costs**
The direct costs consisted of health service costs. The costs included medication, physician and nursing costs, as well as laboratory testing costs for R-Z recipients. The costs of treating adverse events were incorporated into the analysis. The costs of treating an active TB case were also included, as were the costs of contact tracing and treatment. The costs and the quantities were not reported separately. The initial costs of treatment were based on actual data taken from the San Francisco Department of Public Health. The costs of treating an active TB case and of contact tracing and treatment were derived from a study published in 1999. The total costs were derived using modelling. All of the costs were adjusted to 2001 values using the medical care component of the Consumer Price Index. Discounting was applied at an annual rate of 3%, which was appropriate as the costs were incurred for 64 years (or until death).

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was conducted to assess the robustness of the results under different assumptions and changes in input values. The parameters examined were the efficacy of R-Z treatment, the rates of treatment completion, and the percentage of IS-resistant infections. Additional scenarios included duration of IS-therapy equal to 9 months, and routine testing of liver enzyme levels in patients receiving IS. One-way, two-way and threshold analyses were undertaken. The range of values used in sensitivity analysis was based on authors' assumptions.

**Estimated benefits used in the economic analysis**
Without treatment of latent TB-infection in 1,000 persons, 110 cases of TB and 10.8 TB-related deaths would occur.

Compared with no treatment, in a cohort of 1,000 patients, treatment with either R-Z for 2 months or IS for 6 months prevented 29.7 future cases of TB (57.7 cases undiscounted) and 5.1 TB-related deaths, and prolonged survival by 1.2 years.

The benefits were estimated for a period up to 99 years of age (or death).

**Cost results**
The cost of initial treatment per patient was $565 in the R-Z group and $292 in the IS group.

The expected cost of TB treatment and contact tracing and treatment was $1,147 in the R-Z group and $874 in the IS group. For patients receiving no treatment this cost was $1,073 per patient. Thus, for the cohort receiving either IS or R-Z strategies, this cost was reduced to $582 per patient.

The total average costs per patient for IS or R-Z strategies were not reported.

Compared with no treatment, the IS strategy would produce net savings of $199 per patient treated, whereas the R-Z strategy would cost $74 per patient treated. Thus, the net incremental savings of IS for 6 months versus R-Z for 2
months were $273 per patient treated.

The costs of treating adverse events were included in the analysis. The costs were estimated over a patient lifetime (up to 99 years of age or death) and were discounted at 3% annually.

**Synthesis of costs and benefits**

IS was the dominant option compared with R-Z, as it was less costly and equally effective. IS was also the dominant option compared with no treatment, as it was less costly and more effective. R-Z was more effective than no treatment, but at an incremental cost of $2,492 per additional TB case prevented.

Sensitivity analyses showed that, assuming equal efficacy between the two regimens, there was no threshold completion rate for R-Z at which the two treatments would be of equal net cost.

The results were insensitive to changes in R-Z completion rates when the IS completion rate remained at 68%. In contrast, at an IS completion rate of 36% or less (and 68% R-Z completion rate), R-Z would become cost-saving in comparison with IS. R-Z would also be cost-saving relative to IS if its efficacy rose to 90% and its completion rate was 80% or more. In terms of rates of IS-resistant infections, these would have to increase at 42% in order for the two treatments to incur equal total costs per patient. The results were not sensitive to a 9-month duration of IS treatment, or to the routine testing of liver enzyme levels in patients receiving IS.

**Authors’ conclusions**

For patients with latent tuberculosis (TB) infection, treatment with either isoniazid (IS) for 6 months or rifampin-pyrazinamide (R-Z) for 2 months improves survival, compared with no treatment. For latent TB infection in adults without human immunodeficiency virus (HIV) infection, treatment with IS for 6 months was more cost-effective than R-Z for 2 months.

**CRD COMMENTARY - Selection of comparators**

Both interventions assessed in the analysis had been recommended, by US national guidelines, for the treatment of latent TB infection in adults without HIV infection. The comparator of the analysis (IS for 6 months) was selected because it represented the standard treatment for decades, although its use had been limited by toxicity and poor adherence to treatment. You should consider whether the comparator represents routine practice in your own setting.

**Validity of estimate of measure of effectiveness**

The sources of the effectiveness data were a review or synthesis of completed studies and authors’ assumption. It was not stated whether a systematic review of the literature had been undertaken. The authors used data from the available studies selectively. Although this is a common practice with models, it does not always ensure that the best data available are used in the model. One cannot be sure that all relevant literature was identified, although the estimates of effectiveness were derived credibly from the studies identified.

Most evidence on effectiveness was based on data derived from a clinical trial. It is not possible to comment on the internal validity of the trial as details of a power calculation to determine sample size, methods of sampling and blinding were not reported. There were no reported statistical analyses to account for potential biases and confounding factors. However, this information might be available in the parent study (Jasmer et al., see "Other Publications of Related Interest" for bibliographic details).

The authors also used their own assumptions to derive effectiveness. They assumed that the efficacy of R-Z therapy was equal to that of IS administered to patients without HIV infection. They did not justify their assumption, although they cited the lack of efficacy data for adults without HIV infection. The assumption was, however, investigated in the sensitivity analyses.
Validity of estimate of measure of benefit
The estimation of benefits was modelled. The Markov model used for this purpose was appropriate, as it incorporated all possible states following treatment with the interventions assessed and allowed for the estimation of the long-term benefits.

Validity of estimate of costs
It was stated that the study adopted a health service perspective. As such, all the costs relevant to this perspective appear to have been included in the analysis. The costs and the quantities were not analysed separately, and this hinders the generalisability of the results. No sensitivity analysis of the costs was undertaken, which may limit the interpretation of the study findings. Discounting was applied, which was appropriate since the costs were incurred during 35 years. The year to which the prices referred was reported, and this increases the reproducibility of the results.

Other issues
The authors compared their results with those of other relevant studies. The issue of generalisability to other settings was also addressed (see comments on limitations below). The results of the study were reported in full and the authors' conclusions reflected the scope of the analysis.

The authors reported a number of limitations to their analysis. First, it was assumed in the model that the efficacy of R-Z therapy in adults without HIV infection was equal to that of IS therapy. Second, it was assumed in the model that all patients were sensitive to treatment with either R-Z or IS. Third, the study was underpowered to detect a difference in TB case rates between the two treatment groups. Finally, the analysis did not include all costs relevant to an analysis from the societal perspective. Therefore, the authors likely underestimated the true cost-effectiveness of IS therapy and R-Z therapy relative to no treatment. Moreover, they considered as further limitations of the study the restricted applicability of the results to only settings where adequate monitoring and follow-up treatment were possible.

Implications of the study
It can be inferred from the results of the analysis that, in terms of cost-effectiveness, 6 months' IS should be preferred to 2 months' R-Z for the treatment of latent TB infection in adults without HIV. However, the authors suggested that in settings in which long-term adherence to treatment could not be assured, and where the completion rate of IS treatment might be significantly less than that of R-Z therapy, treatment with R-Z might be the preferred option.

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Other publications of related interest

Rose DN. Short-course prophylaxis against tuberculosis in HIV infected persons: a decision and cost-effectiveness

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