Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States
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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
Three alternative strategies for the management of latent tuberculosis (TB) infection in immigrants were examined. The strategies comprised tuberculin testing followed by one of three treatments for those with a positive test result:

- 300 mg isoniazid plus 25 mg pyridoxine daily for 9 months;
- 600 mg rifampin daily for 4 months; or
- 600 mg rifampin plus 15 to 20 mg pyrazinamide per kg of body weight daily for 2 months.

Type of intervention
Screening and treatment.

Economic study type
Cost-effectiveness and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of documented immigrants, aged 18 years or older, who entered the USA from developing countries.

Setting
The setting was not stated. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data came from studies published between 1982 and 2000. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies and several assumptions.

Modelling
A decision analytic model was constructed to represent the clinical and economic outcomes associated with the four strategies under evaluation. The time horizon of the model was lifetime. Thirteen geographically independent regions of the world were considered. Further details on the model were not provided.

Outcomes assessed in the review
Some of the outcomes were derived from the literature:

- the sensitivity and specificity of the tuberculin skin test;
- the effectiveness of isoniazid, rifampin and rifampin-pyrazinamide;
- the probability of adverse drug reactions (uncomplicated hepatitis, complicated hepatitis, others); and
- the probability of death.

The number of immigrants entering the USA annually, the prevalence of TB in each region, and the number of TB cases in the USA were derived from official statistics.

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

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

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

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

**Number of primary studies included**
Most of the effectiveness evidence came from 11 primary studies.

**Methods of combining primary studies**
Not stated.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The sensitivity of the tuberculin skin test was 0.99 (range: 0.98 - 1) and the specificity was 0.90 (range: 0.85 - 0.90).

The effectiveness was 0.70 (range: 0.56 - 0.84) for isoniazid, 0.70 (range: 0.56 - 0.84) for rifampin and 0.75 (range: 0.60 - 0.90) for rifampin-pyrazinamide.

The probability of uncomplicated hepatitis was 0.030 (range: 0.015 - 0.045) for isoniazid and 0.083 (range: 0.042 - 0.125) for rifampin-pyrazinamide.

The probability of complicated hepatitis was 8.976 x10^-5 (range: 7.181 x10^-5 - 1.220 x10^-4) for isoniazid and 2.455 x10^-4 (range: 1.841 x10^-4 - 3.069 x10^-4) for rifampin-pyrazinamide.

The probability of other adverse drug reactions was 0.173 (range: 0.121 - 0.225) for isoniazid, 0.122 (range: 0.085 - 0.159) for rifampin and 0.149 (range: 0.104 - 0.194) for rifampin-pyrazinamide.
The probability of death was 0.0563 (range: 0.0507 - 0.0619).

**Methods used to derive estimates of effectiveness**
A panel of three infectious disease specialists with expertise in TB made some assumptions.

**Estimates of effectiveness and key assumptions**
The panel of experts assumed that the health-related quality of life was 0.627 (range: 0.6 - 0.650) for acute illness and 0.896 (range: 0.875 - 0.925) for convalescence. Further assumptions were:

- the prevalence of latent infection among new immigrants reflected the prevalence of infection in their country of origin;
- drug-resistance patterns among new immigrants reflected resistance patterns observed in foreign-born persons in whom active disease developed within 5 years of entry into the USA;
- deaths from active TB infection occurred, on average, within 2 months of the initial diagnosis.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the quality-adjusted life-years (QALYs) in the cost-utility analysis and the number of future cases of active TB in the cost-effectiveness analysis. The utility data were derived from experts’ opinions, while the survival data came from official mortality statistics. The total QALYs were obtained from the decision model. Future benefits were discounted at an annual rate of 3%.

**Direct costs**
A 3% annual discount rate was applied since the costs were incurred during a long time. The unit costs were not presented separately from the quantities of resources used. The health services in the economic evaluation were medications, visits, tests, treatment for TB infection, transportation, interpreters, adverse reactions and hospitalisation. The cost/resource boundary reflected the societal perspective adopted in the study. Resource use was estimated from assumptions and some published studies. The unit costs came from the Medicare reimbursement rates and published studies. All the costs were inflated to 2000 values using the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were considered since a societal perspective was adopted in the study. The time spent in travel and receiving medical care was calculated. The indirect costs were presumably treated as direct costs in that a 3% annual discount rate was applied and the price year was 2000. The unit costs and the quantities of resources used were not presented separately. The costs were estimated from national data on the median salaries of foreign-born persons living in the USA. The source of the quantity of the patients’ time was not reported.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were carried out to address the robustness of the cost-effectiveness ratios to variations in almost all model inputs. Plausible ranges, mostly derived from the literature, were used. It appears that threshold analyses were carried out. A Monte Carlo simulation was also performed and all variables were varied simultaneously with values.
drawn from a probabilistically weighted triangular distribution.

**Estimated benefits used in the economic analysis**
The number of future cases of active TB (and QALYs) with no intervention, isoniazid, rifampin and rifampin-pyrazinamide were:

for China, no intervention 888 (0), isoniazid 296 (1,652), rifampin 268 (1,730) and rifampin-pyrazinamide 212 (1,886);

for the Philippines, no intervention 1,782 (0), isoniazid 594 (3,315), rifampin 535 (3,480) and rifampin-pyrazinamide 424 (3,789);

for South Korea, no intervention 262 (0), isoniazid 90 (480), rifampin 87 (488) and rifampin-pyrazinamide 70 (536);

for Vietnam, no intervention 2,072 (0), isoniazid 774 (3,622), rifampin 618 (4,057) and rifampin-pyrazinamide 515 (4,345);

for East Asia and the Pacific, no intervention 694 (0), isoniazid 208 (1,356), rifampin 204 (1,367) and rifampin-pyrazinamide 162 (1,484);

for India, no intervention 971 (0), isoniazid 283 (1,920), rifampin 300 (1,872) and rifampin-pyrazinamide 250 (2,012);

for South Asia, no intervention 368 (0), isoniazid 119 (695), rifampin 114 (709) and rifampin-pyrazinamide 93 (767);

for Mexico, no intervention 3,543 (0), isoniazid 972 (7,174), rifampin 1,044 (6,973) and rifampin-pyrazinamide 889 (7,406);

for Haiti, no intervention 721 (0), isoniazid 241 (1,339), rifampin 219 (1,401) and rifampin-pyrazinamide 178 (1,515);

for Latin America and the Caribbean, no intervention 1,236 (0), isoniazid 357 (2,453), rifampin 373 (2,408) and rifampin-pyrazinamide 303 (2,603);

for Eastern Europe and Central Asia, no intervention 378 (0), isoniazid 105 (762), rifampin 112 (742) and rifampin-pyrazinamide 89 (289);

for the Middle East and North Africa, no intervention 343 (0), isoniazid 100 (678), rifampin 108 (656) and rifampin-pyrazinamide 89 (709); and

for Sub-Saharan Africa, no intervention 675 (0), isoniazid 203 (1,317), rifampin 200 (1,325) and rifampin-pyrazinamide 160 (1,437).

**Cost results**
The estimated costs (in millions of dollars) with no intervention, isoniazid, rifampin and rifampin-pyrazinamide were:

for China, no intervention $21.7, isoniazid $15.7, rifampin $16.8 and rifampin-pyrazinamide $16;

for the Philippines, no intervention $43.5, isoniazid $27.9, rifampin $29.3 and rifampin-pyrazinamide $27.5;

for South Korea, no intervention $6.4, isoniazid $6.2, rifampin $6.9 and rifampin-pyrazinamide $6.8;

for Vietnam, no intervention $50.6, isoniazid $29.8, rifampin $28.2 and rifampin-pyrazinamide $26.5;

for East Asia and the Pacific, no intervention $17, isoniazid $14.8, rifampin $16.8 and rifampin-pyrazinamide $16.4;

for India, no intervention $23.7, isoniazid $15.7, rifampin $18 and rifampin-pyrazinamide $17.4;
for South Asia, no intervention $9, isoniazid $7.7, rifampin $8.6 and rifampin-pyrazinamide $8.4;

for Mexico, no intervention $84.3, isoniazid $60.9, rifampin $69.7 and rifampin-pyrazinamide $68.2;

for Haiti, no intervention $17.6, isoniazid $10.8, rifampin $11.3 and rifampin-pyrazinamide $10.6;

for Latin America and the Caribbean, no intervention $30.2, isoniazid $35.2, rifampin $40.8 and rifampin-pyrazinamide $40.9;

for Eastern Europe and Central Asia, no intervention $9.2, isoniazid $13.7, rifampin $16 and rifampin-pyrazinamide $16.1;

for the Middle East and North Africa, no intervention $8.4, isoniazid $9, rifampin $10.4 and rifampin-pyrazinamide $10.4; and

for Sub-Saharan Africa, no intervention $16.5, isoniazid $10.9, rifampin $12.1 and rifampin-pyrazinamide $11.5.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the study interventions. The analysis showed that all treatment strategies were more effective and less costly than no intervention. In addition, treatment with rifampin alone was always dominated by treatment with rifampin-pyrazinamide. In particular, treatment with rifampin-pyrazinamide was the dominant strategy in the Philippines, Vietnam and Haiti. Treatment with isoniazid was cost-saving in China, South Korea, East Asia and the Pacific, India, South Asia, Mexico and Sub-Saharan Africa. Finally, treatment with rifampin-pyrazinamide was a highly cost-effective strategy for the remaining developing countries (Latin America and the Caribbean, Eastern Europe and Central Asia, and Middle East and North Africa).

The sensitivity analyses showed that if the effectiveness of isoniazid was at least 22% greater than that of rifampin-pyrazinamide in immigrants from Vietnam, or at least 16% greater in immigrants from Haiti or the Philippines, then isoniazid would become the preferred strategy for those nations. Drug price represented a further key variable. The Monte Carlo simulation showed that the treatment strategies recommended in the analysis were dominated only in 5% of all simulations performed. Consequently, the results of the main analysis were robust.

**Authors' conclusions**

Screening immigrants from developing countries for latent tuberculosis (TB) infection at the time of their entry into the USA, with further treatment of those testing positive, represented a cost-effective strategy for all countries. Due to the high resistance to isoniazid, treatment with rifampin-pyrazinamide should be the preferred option for Vietnam, Haiti and the Philippines.

**CRD COMMENTARY - Selection of comparators**

The authors provided a justification for the choice of the comparators. The selection of no intervention as the baseline comparator was appropriate to assess the net economic and clinical value of the alternative strategies under evaluation. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

It was not stated whether a systematic review of the literature was carried out. It appears that the primary studies may have been identified selectively. Information on the design and the patients included in the primary studies was not provided. It was unclear how the primary estimates were combined and whether the authors considered differences across the primary studies. Some key assumptions were also made on the basis of a panel of experts. However, the methods used to reach consensus were not described. Therefore, it is difficult to estimate the validity of the effectiveness estimates that were used in the decision model. The authors performed several sensitivity analyses to deal with the issue of uncertainty in the model inputs. This permitted the identification of those inputs that had a strong impact on the estimated results.
Validity of estimate of measure of benefit
The authors used two summary benefit measures, QALYs for the cost-utility analysis and cases of active TB for the cost-effectiveness analysis. Both of these appear to have been appropriate. Discounting was relevant and was carried out. In particular, the use of QALYs enables comparisons to be made with the benefits of other health care interventions.

Validity of estimate of costs
A societal perspective was adopted and both the direct and indirect costs were included in the economic evaluation. The price year was reported, thereby facilitating reflation exercises in other settings. The source of the cost data was provided for most cost items. However, information on resource consumption was scarce. The costs were treated deterministically in the base-case, although probabilistic distributions were assigned to all economic parameters in the Monte Carlo simulation. Likewise, in the analysis of effectiveness, the sensitivity analyses helped identify the most relevant inputs. Discounting, which was relevant, was performed.

Other issues
The authors did not compare their findings with those from other studies. However, they did address the issue of the generalisability of the study results to other settings. The authors stressed that their findings of effectiveness could be extrapolated to other countries, but the economic analysis was specific to the US setting. Caution is therefore required when interpreting the conclusions of the analysis. It was also noted that the analytic framework used for TB infection could be used for other infectious diseases. The authors noted some limitations of their study. First, it was not possible to distinguish between documented immigrants and other foreign-born persons. Second, no population-level data were available on the hepatotoxicity of daily rifampin-pyrazinamide. Third, it was assumed that cultural differences among immigrants were unrelated to adherence and thus to the effectiveness of drug regimens. Fourth, data on resistance referred to 1996 to 2000 programmes and might not reflect current global trends. Finally, data on the effectiveness of rifampin-pyrazinamide in patients with resistance to either drug, were not available.

Implications of the study
The study results suggested that, in a globalised world, the ultimate success at eliminating TB infection depends on cooperation across nations in order to attend global disparities in the burden of this disease.

Source of funding
None stated.

Bibliographic details

PubMedID
12466510

DOI
10.1056/NEJMs021099

Indexing Status
Subject indexing assigned by NLM

MeSH
Antitubercular Agents /economics /therapeutic use; Cost Savings; Decision Support Techniques; Drug Resistance, Bacterial; Emigration and Immigration; Health Care Costs; Humans; Mass Screening /economics; Prevalence;
Tuberculosis /diagnosis /drug therapy /economics /ethnology: United States /epidemiology

**Accession Number**
22003008019

**Date bibliographic record published**
31/08/2004

**Date abstract record published**
31/08/2004