Tuberculosis prevention in methadone maintenance clinics: effectiveness and cost-effectiveness

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
An intervention programme to provide screening for tuberculosis infection, medical evaluation, and directly observed preventive therapy (DOPT) in methadone maintenance clinics in a population of injection-drug users at high risk for tuberculosis and HIV infection. There was a division of labour between the methadone maintenance clinics and the tuberculosis clinics. Tuberculosis skin testing, HIV counselling and testing, tuberculosis and HIV education, and DOPT were performed in the methadone maintenance clinics. Medical evaluation of referrals from the methadone maintenance clinics (those with TST 5 mm or greater, as well as those with a prior history of positive TST) and decisions on which patients were eligible for preventive therapy, were performed in the tuberculosis clinics. Tuberculin skin testing (TST) by the Mantoux method. Patients were classified as TST reactors in the tuberculosis clinics if they fulfilled one of the following criteria: a prior history of positive TST, a TST of 10 mm or greater and HIV-seronegative, and a TST of 5 mm or greater and HIV-seropositive or their HIV serostatus was unknown. All TST reactors were further evaluated for tuberculosis. Patients who were excluded for tuberculosis were recommended for isoniazid preventive therapy if there was no contraindication. The main components of the intervention programme were coordination between the methadone maintenance clinic and the tuberculosis control programme at the administrative, staffing, and service delivery levels. Also the use of methadone maintenance clinic staff to observe the ingestion of medications and the use of incentives (the provision of DOPT along with the daily methadone dosing) and enablers. Enablers included bus tokens or transportation to the clinic, food and juice, shorter waiting-time at the clinic, and the use of community health workers to facilitate the process of medical evaluation and to follow up rapidly lapses with DOPT.

Type of intervention
Screening and primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Injection-drug users at high risk for tuberculosis and HIV infection.

Setting
Hospital. The economic study was carried out in California, USA.

Dates to which data relate
Effectiveness and resource use data were mainly based on the data collected by the HIV-related Tuberculosis Prevention (HRTP) Project over 6 years (January 1990 to December 1995). Some clinical probabilities were obtained from the literature published between 1970 and 1997. Unpublished data from a prospective study of patients with tuberculosis (the dates of which were not reported) was used to derive data on the proportion hospitalised. The price
year was 1998.

**Source of effectiveness data**
The evidence for final outcomes was based on a single study and a literature review.

**Link between effectiveness and cost data**
Costing for the intervention programme appears to have been undertaken retrospectively on the same study sample as that used in the effectiveness analysis.

**Study sample**
Power calculations were not used to determine the sample size. The study sample consisted of a total of 2,689 clients of whom 18% were HIV-seropositive, 63% were HIV-seronegative, and 19% had unknown HIV serostatus. The sample had a median age of 40 year (range: 18 - 77) and were screened at least once between 1990 and 1995. A total of 1,060 subjects received 2,309 repeat screenings. Clients with a negative TST received repeat TST annually. The overall TST conversion rates for HIV-seropositives was 3.1/100 person-years (PY), for HIV-seropositives was 2.4/100 PY, and for clients with unknown HIV serostatus was 0.4/100 PY.

**Study design**
This was a prospective cohort study, carried out in five centres. The duration of the follow-up was 3 years. The proportion of patients who were lost to follow-up or who refused their medication was less than 10%.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness appears to be treatment completers only. The programme effectiveness was determined by completion rates of tuberculin skin testing, medical evaluation, and preventive therapy. The number of active cases of tuberculosis identified through screening was determined as well.

**Effectiveness results**
99% of patients received TST, 96% underwent medical examination, 91% began isoniazid preventive therapy, and 82% completed preventive therapy. Over a 3-year follow-up period only one case of tuberculosis was identified among the 453 TST reactors screened.

**Clinical conclusions**
The HRTP Project in San Francisco, based in methadone maintenance clinics, is a highly effective model of tuberculosis prevention in a population at high risk for tuberculosis and HIV infection. Because of the effective implementation of the HRTP Project, the programme was effective in preventing tuberculosis among its clients.

**Modelling**
A four-stage Markov process with a 1-year cycle was developed to estimate costs and effects associated with each alternative strategy in the TST reactor population over 3 and 10 years of follow-up. The input data for the model were derived from the screening programme and a review of the literature.

**Outcomes assessed in the review**
Outcomes were also derived from a literature review:

- annual probability of developing tuberculosis, recent converter and remote infection;
probability of death with tuberculosis (first year);

annual all-cause probability of death;

efficacy of isoniazid-preventive therapy (annual reduction in probability of developing tuberculosis) by duration of prophylaxis (less than 6 months, 6 to 11 months, and 12 months and over).

**Study designs and other criteria for inclusion in the review**
The data for HIV-seronegative, TST converters were derived from studies of individuals who were not injection-drug users. Controlled clinical trials in HIV-seronegative individuals were used to derive the efficacy of isoniazid preventive therapy.

**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**
A total of 8 studies were included.

**Methods of combining primary studies**
Each clinical probability was based on a single study.

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

**Results of the review**
The outcomes derived from the literature for individuals who are HIV-seropositive and HIV-seronegative, respectively, were as follows:

the annual probability of developing tuberculosis, (recent converter), 0.054 and 0.011;

the annual probability of developing tuberculosis (remote infection), 0.045 and 0.010;

probability of death with tuberculosis (first year), 0.350 and 0.165;

annual all-cause probability of death, 0.108 and 0.0031;

efficacy of isoniazid-preventive therapy by duration of prophylaxis: 0.21 for less than 6 months, 0.69 for 6 to 11 months, and 0.93 for 12 months and over (similar for both seronegative and seropositive-HIV individuals).

**Measure of benefits used in the economic analysis**
The number (percentage) of cases of tuberculosis prevented and tuberculosis-related deaths prevented over 3 and 10
years of follow-up were the benefit measures used in the economic analysis. They were calculated using a Markov process with input data coming from the screening programme and a literature review.

**Direct costs**
Costs were discounted. Quantities were reported separately from the costs. Cost components were reported separately. The cost analysis covered the costs of the intervention programme and costs averted due to prevention of tuberculosis cases. The variable costs of the intervention programme consisted of labour and supplies for provision and interpretation of TST, labour for provision of DOPT, medical evaluation of TST reactors including chest radiograph, incentives and enablers, bacteriologic tests for TB suspects, liver function tests, medical evaluation for adverse reaction, and one month supply of isoniazid. The corresponding fixed costs comprised a project manager, community health worker, and a clerk who provided clerical support. Costs associated with averted cases of tuberculosis comprised the costs of diagnosis, treatment, and contact investigation associated with the active cases prevented in the cohort of clients over a hypothetical 10-yr period, as well as the cost of treating active cases developing among infected contacts. The perspective adopted in the cost analysis was that of a local tuberculosis control programme, but also included costs of inpatient treatment for tuberculosis. The source of unit cost data for the components of the intervention programme was the study institution. A weighted average cost was calculated for the outpatient treatment cost using published data in 1995 based on determining drug-resistance rates among clients with tuberculosis in California with a history of injection-drug use. Unpublished data from a prospective study of patients with tuberculosis was used to derive data on the proportion hospitalised. A hospital-specific cost-to-charge ratio was used to derive costs based on hospital charges. All the relevant data for contact investigation and associated infection-related treatment was based on the data collected by the tuberculosis control programme. The price date was 1998. The medical care services component of the US Consumer Price Index was used to adjust costs to 1998 prices.

**Indirect Costs**
Not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
A set of one-way sensitivity analyses was performed based on excluding savings from contact tracing and treatment, reducing the percentage of patients with active tuberculosis hospitalised, and a reduction in effectiveness of the intervention programme.

**Estimated benefits used in the economic analysis**
Over the first 3-year follow-up period, only one case of tuberculosis was identified among the 453 TST reactors screened, yielding a prevention rate of 95% of expected tuberculosis cases (based on 20 (19.4 discounted) cases of expected tuberculosis). The number of expected cases of tuberculosis over 10 years of follow-up without the screening programme was estimated to be 57.7 cases. The screening programme was estimated to prevent 30 (28.1 discounted corresponding to 48.7%) cases of tuberculosis. The number of tuberculosis-related deaths prevented over 10 years of follow-up was 7.6. The discount rate applied to the cases of tuberculosis prevented was 3%.

**Cost results**
The discount rate was 3%. The total programme cost was $771,569 but prevented costs totalling $876,229, yielding a net saving of $104,660.

**Synthesis of costs and benefits**
The net average saving (costs) per case prevented was $3,724. The sensitivity analysis had a range of cost per case
prevented from a saving of $6,674 to a cost of $12,677.

**Authors' conclusions**
The study demonstrates that, when effectively implemented, screening for tuberculosis infection and DOPT in methadone maintenance clinics is a highly cost-effective approach in preventing tuberculosis.

**CRD COMMENTARY - Selection of comparators**
The reason for the choice of the comparator (a policy of no screening) is clear. This allowed the active value of the treatment to be evaluated.

**Validity of estimate of measure of effectiveness**
The internal validity of the effectiveness results can not be reasonably guaranteed due to the retrospective nature of the study design. Also, there is no evidence as to the thoroughness of the literature review or the quality assessment of the primary studies included. No justification was provided for adopting each clinical probability from a single study. The study sample for the single study appears to be representative of the study population.

**Validity of estimate of measure of benefit**
The estimation of benefits was based both on the effectiveness analysis and on modelling using a Markov process.

**Validity of estimate of costs**
Quantities were reported separately from the costs and adequate details of the methods of cost estimation were given. All relevant direct costs appear to have been included in the cost analysis. Cost-to-charge ratio was used where appropriate. Statistical analysis was not performed on either resource use data or cost data. The price year was specified and future costs were discounted. The impacts of the intervention programme on indirect costs (lost productivity), which appear to be relevant in the context in question, were not addressed.

**Other issues**
Given the retrospective nature of the study design, and the possible lack of a comprehensive literature review and extensive sensitivity analysis, some degree of caution may need to be exercised in the interpretation of the study results. The issue of generalisability to other settings or countries was not addressed. Some comparisons were made with other studies. The study sample consisted of injection-drug users and the authors’ comment appears to reflect that. According to the authors, the study had the following limitations: the rates of tuberculosis (for various populations) adopted from the literature may not be directly applicable to the study population (injection-drug users); it was speculated that because of lack of data on the efficacy of isoniazid preventive therapy in HIV-seropositive individuals, the rate applied in the study may have overestimated the efficacy, especially since 5% of the injection-drug users with tuberculosis in San Francisco from 1993 to 1996 had isoniazid resistant disease; the figure used in the analysis for the rate of TB-related hospitalisation (81%) may overestimate the actual proportion hospitalised (it was reported that at the time of the study no published US data on this parameter existed), leading to an overestimation of the cost-effectiveness of the intervention programme.

**Implications of the study**
The key programme components such as coordination between public health and methadone maintenance programmes and the use of incentives and enablers are probably essential for ensuring programme effectiveness. This study provides a guide for planning, implementing and evaluating tuberculosis screening and DOPT programmes in methadone maintenance clinics.

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