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Direct costs of three models for the screening of latent tuberculosis infection

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Abstract

Aim: to compare the direct costs of three models for detection of latent TB infection (LTBI) in routine clinical practice in Switzerland

Method: comparison of the overall costs of screening for LTBI, including medical and radiological examination, and preventive treatment associated with three screening models. Model 1 relies only on the tuberculin skin test (TST) as per the current national guidelines, Model 2 on T-SPOT.*TB* only and Model 3 on TST followed by confirmation of positive results by T-SPOT.*TB.* Costs were taken directly from the clinic's figures. Clinical assumptions were based on the 267 patients who were referred to the clinic over the study period.

Results: Model 3 was the most cost-effective. Using only the skin test (Model 1) was the least cost-effective. If only one test for LTBI is used, then Model 2 (using T-SPOT.*TB* only) is cheaper than using the TST (Model 1).

Conclusions: Screening for LTBI by TST followed by confirmation with T-SPOT.*TB* is less costly than screening with TST alone, as it allows a reduction in the number of people who receive preventive treatment. In groups with a high proportion of negative TSTs, screening with T-SPOT.*TB* test only may be the most cost-effective.

Introduction

A key component of TB control is the targeted identification and treatment of people carrying a latent TB infection (LTBI), who are at elevated risk of progression to active TB disease (1). We have, so far, relied on the Tuberculin Skin Test (TST) to identify those infected who would benefit from treatment. The recent advent of a rapid technique for detecting antigen-specific T-Cells direct from blood offers a new approach for detecting *M. tuberculosis* infection (2;3). The T-SPOT.*TB* test is the regulatory-approved version of the ex vivo enzyme-linked immunospot (ELISPOT) assay for the detection of activated T-Cells specific for ESAT-6 and CFP-10 (4). These antigens are present in *M. tuberculosis* but absent from Bacillus Calmette-Guerin (BCG) and most environmental mycobacteria (5;6). The test is a sensitive and specific marker of *M. tuberculosis* infection, gives uniformly negative results in healthy unexposed controls (irrespective of BCG vaccination status), and correlates with *M. tuberculosis* exposure among contacts (7-17). Given the lack of a gold-standard for latent TB infection, these results strongly suggest that this may be a more accurate test than the TST. Other new blood tests using different methodologies based on the principle of detecting interferon-gamma released in response to stimulation by ESAT-6 and CFP-10 have also been shown to be able to effectively discriminate TB infection from prior BCG vaccination (18;19).

As a result of this clinical evidence, there have been growing calls to implement new blood tests into routine clinical practice. However, to date, there has been no published evidence on the cost implications of doing so.

The purpose of this study is not to examine the absolute cost-effectiveness of LTBI treatment and screening programs *per se*, but rather to examine the particular question of whether the new blood test for detection of LTBI (T-SPOT.*TB*) is cost-effective relative to existing programs based upon the TST for screening recent contacts of infectious active TB patients. The study was designed to be based on actual clinical and cost data, and to examine the direct costs of implementation of this new blood test to the healthcare provider in terms of their overall budget for latent TB screening and treatment.

Materials and Methods

Participants

The data for the analysis came directly from the use of the Tuberculin Skin Test (TST) side-by-side with T-SPOT.*TB* under routine program conditions at the University Medical Policlinic Lausanne (UMPL). We have been running a study to compare the performance of the two tests in a number of population groups including recent contacts of infectious TB patients. All contacts presenting to the UMPL between January 2004 and December 2005 were included in this study. A total of 267 participants were included in the study. 144 were Swiss-born; the majority of the foreign-born were immigrants from high incidence countries. 168 had known BCG vaccination histories, with 89.9% (151/168) having received the BCG vaccine.

The TST was applied using the Mantoux method using 2TU of RT23 PPD, according to the Swiss National Guidelines (20). Results are read at 72 hours and considered positive if induration ≥10mm. All TSTs were placed and interpreted by experienced operators. For the T-SPOT.*TB* test, a 10ml blood sample was taken and analyzed in a local analytical laboratory (BBR-LTC laboratories). The cutoff for the assay was 6 spots, according to the manufacturer's instructions (Oxford Immunotec, UK).

According to the Swiss National Guidelines, contacts with a TST > 10 mm are offered a preventive treatment with isoniazid for 9 months. Contacts who refuse the preventive treatment are offered a clinical follow-up for 2 years.

The raw data on the results of both tests, used in the subsequent cost-effectiveness analysis, are shown in **Table 1**. Of the 267 contacts, 193 (or 72.3%) were positive by TST. 74 (27.7%) were positive by T-SPOT.*TB*. Only 33.7% (65/193) of the TST positive individuals were also

positive by the T-SPOT.*TB* test. There were 9 individuals who were T-SPOT.*TB* positive and TST negative.

Models

A simple decision-tree analysis was constructed representing different possible clinical pathways for the diagnosis and subsequent treatment of latent TB infection (LTBI), as shown in **Figure 1**. Three scenarios were modelled; Model 1 captures current practice where the TST is used as the only tool to diagnose LTBI, Model 2 calculates the costs of using T-SPOT.*TB* alone as the only tool to diagnose LTBI (i.e. a complete replacement for the TST) and Model 3 calculates the costs of using the TST for the initial screening of patients, followed by a T-SPOT.*TB* test in all TST positive individuals prior to treatment. The clinical and cost-effectiveness basis for Model 3 has also been put forward by the UK National Institute for Clinical Excellence (NICE) in draft guidelines for the implementation of new blood tests for Tuberculosis (21).

Each model was run for a hypothetical cohort of 1,000 patients, with the model inputs for the test results directly extrapolated from the actual results shown in **Table 1**. All calculations were set-up and calculated on a purpose-built Microsoft Excel spreadsheet.

The models represent a direct-cost analysis from the point of view of the healthcare provider. No consideration is given to costs and quality-of-life losses on the part of the patient; in addition, no consideration is given to wider transmission of TB in the community. No time discounting was necessary, as all the costs in each clinical pathway were assumed to be incurred during a one year period. We also did not account for the costs of repeated TSTs, which are in practice often administered in dubious or potentially boosted cases.

Costs were taken directly from the published dispensary costs at the UMPL as shown in **Table 2**, and expressed in both Swiss Francs (CHF) and Euros (at a rate of CHF1 = €0.645). The costs of LTBI treatment include an initial chest X-ray to rule out active TB prior to treatment, the costs of 9 months of isoniazid and the costs of clinician visits and liver function tests during the treatment period. Costs associated with bacteriological examination of sputum, if indicated, and side-effects from isoniazid treatment were ignored. All patients in whom preventative therapy was indicated were assumed to complete the full course of therapy. As no reimbursement amount has yet been established in Switzerland for the T-SPOT.*TB* test, a figure of CHF200 (€129) was taken as an initial sum taken to estimate the costs of the test, associated consumables and labour required to perform the test both in the laboratory and the physician's office. The costs of the T-SPOT.*TB* test were subsequently explored in a sensitivity analysis.

Results

Figure 1 shows how the costs, combined with the actual clinical data, allow the full costs of each clinical pathway to be calculated. The total cost of the TST only pathway (Model 1) is CHF1,078,790 (€695,820); the initial cost of screening 1,000 contacts with the TST of CHF35,000 (€22,575) and the costs of subsequently treating the 723 TST positive individuals for LTBI at CHF1,043,790 (€673,245). The overall cost of using T-SPOT.*TB* only (Model 2) is lower at CHF600,210 (€387,135) as although the initial costs of screening are higher, fewer people receive treatment. As treatment costs are substantially higher than the costs of screening by either test, this results in an overall cost saving. Model 3 is the cheapest of all, costing CHF435,225 (€280,720) for 1,000 patients.

These results show that the costs of an LTBI screening and treatment program, targeted solely at high risk groups, currently costs CHF1,079 (€696) per patient. Switching solely to the T-SPOT.*TB* test, in place of the TST would reduce costs by 44.4% and using both tests together according to the clinical pathway in Model 3, would reduce costs by 59.7%.

A sensitivity analysis of the cost of the T-SPOT.*TB* test was also performed (shown in **Table 4**); which calculated the overall cost of the T-SPOT.*TB* test at which Model 2 and Model 3

respectively would become cost neutral to the current testing paradigm (Model 1). The results show that if T-SPOT.*TB* was used as a direct replacement for the TST it would be cost neutral at an overall cost of CHF679 (€438). If T-SPOT.*TB* was used as a subsequent test after an initial TST, this strategy would be cost neutral at an overall cost for T-SPOT.*TB* of CHF2,844 (€1,834). For completeness, the cost of T-SPOT.*TB* at which Model 2 would become dominant was CHF35.

As we recorded the induration size for the TSTs, we were also able to model the effect of applying different TST cutoffs on the resulting cost of the three screening strategies. The results are shown in **Figure 2**. Results with TST cut-offs of 5mm, 6mm and 15mm were calculated from the clinical data, as these cut-offs correspond to those used in other European countries. The costs of Model 2 (T-SPOT.*TB* only) clearly do not change with TST cutoff as this screening strategy does not involve the TST. However, as increasing TST cutoff decreases the numbers of people deemed to be infected, the costs of both Model 1 and Model 3 decrease with increasing the cutoff size from 10mm to 15mm (to 75% and 59% over the 10mm totals respectively). Decreasing the TST cut-off from 10mm to 5mm increases the costs of Model 1 and Model 3 although this effect is relatively small (a 10% and 6% increase respectively). Nonetheless, at all TST cutoffs modeled, the relative costs of each screening strategy were consistent; with Model 3 being the cheapest, followed by Model 2 and lastly by Model 1. As higher TST cutoffs increase the specificity of the TST at the cost of sensitivity, we also calculated the proportion of the cohort who were T-SPOT.*TB* positive, but TST negative; as a surrogate for the risk of TST false-negatives. The risk of TST false-negatives increased from 1.9% to 10.1% as the TST cutoff is raised from 5 to 15mm.

Discussion

Previous cost-effectiveness methodologies for LTBI screening and treatment have used iterative Markov processes to examine the overall costs to the healthcare system over periods of 15-20 years (22-28), and have included the costs of TB reactivation and drug side-effects, with or without including the costs of loss of quality-of-life and the costs of wider TB transmission. We chose instead to focus only on direct costs over a much shorter time period, for a number of reasons.

Firstly, we wished the model to only use actual clinical data, rather than epidemiological assumptions derived from the literature that may or may not accurately reflect the local situation (29). By taking this approach, we were able to use the clinical results of our 2-year long comparison of both tests side-by-side. The results therefore reflect the reality of the TB screening and treatment program in a low-incidence region like Lausanne.

Secondly, many individual hospitals and public health services, faced with increasing pressure on healthcare costs and a fixed annual budget to provide TB control, will quite legitimately be examining how the introduction of new technology will impact their annual budget, rather than the overall costs of TB to wider society over a 20-year time frame. The restriction of our model to a simple clinical pathway enables healthcare payers to quickly calculate the actual direct costs of implementing the T-SPOT.*TB* test and how it will affect their yearly budget for TB control.

Lastly, the simplicity of the model construction allows the model to be quickly and easily applied to different geographical locations and screening situations, based on actual clinical data that can be easily obtained from pilot studies.

The results of this study demonstrate that the cheapest clinical pathway in all situations modeled was Model 3; using an initial TST followed by T-SPOT.*TB* only in TST positive individuals. This finding is consistent with the findings and recommendations presented in the UK NICE Guidelines (21). It is interesting that this overall conclusion is not affected by the TST cutoff used; and makes the findings from this study potentially applicable to different countries where different TST cutoffs are used. Clearly the potential difficulty of implementing Model 3 into clinical practice is that it doesn't take into account people who may be TST negative, but T-SPOT.*TB* positive. These people may be at risk of TB reactivation, but would not receive treatment. In the cohort examined at Lausanne this was not a significant factor as there were only 9 such individuals in the 267 contacts, representing 3.3% of all results.

However, if populations are considered where the TST suffers from considerable anergy (for example young children, HIV, and other immunosuppressed patients), where it is likely that T-SPOT.*TB* will identify truly infected patients missed by the TST (17;30-32), then Model 3 may no longer be appropriate. Clearly, this argument would also apply to other populations where there is a hidden risk of immunosuppresssion, such as immigrants with a high-probability of undeclared HIV infection. In addition, our results show that in situations where higher TST cutoffs are used, the risk of false-negative TST results can be significant; 10.1% of our study cohort would have been considered infected by T-SPOT.*TB* but not by the TST, had a cutoff of 15mm been used. To truly understand the cost saving that would result from using T-SPOT.*TB* in these populations, either on its own (Model 2) or according to another clinical algorithm, would require a Markov-type analysis that could compute the cost-savings from the cases of TB averted by early identification and treatment of people at high risk of reactivation. This was outside the scope of this study, but this is clearly an important area for future research.

To our knowledge, this is the first analysis of the costs of using a new blood test for TB infection. Although the detailed costs may change, we believe that the overall results are likely to be applicable to any developed world setting where there is a high proportion of positive TST results, many of whom are due to prior BCG vaccination in adults (33) and children (34) and where the main cost of the TB control program is thus due to preventive treatment of individuals identified to be infected by the TST. The results show that using T-SPOT.*TB* is likely to bring about substantial direct cost savings in TB control programs.

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Tables and Figures

	TST +ve	TST –ve	Totals	
T-SPOT.*TB* +ve	65	9	74	28%
T-SPOT.*TB* -ve	128	65	193	72%
Totals	193	74	**267**	
	72%	28%		

Table 1 – Comparative results of the TST and T-SPOT.*TB* tests in all 267 contacts using a TST cutoff of 10mm.

Cost of the skin test	CHF 35	€ 23
Cost of the T-SPOT.*TB* test	CHF 200	€ 129
Cost of LTBI treatment		
10 clinician visits @ 58CHF per visit	CHF 580	€ 374
1 chest X-ray to rule out active TB	CHF 63	€ 41
3 liver function tests @ 18CHF	CHF 54	€ 35
Isoniazid for 9 months	CHF 747	€ 482
TOTAL	CHF 1,444	€ 931

Table 2 – Costs of LTBI tests and treatment used as inputs for cost-effectiveness models. Costs were converted from Swiss Francs into Euros at an exchange rate of 1CHF = €0.645

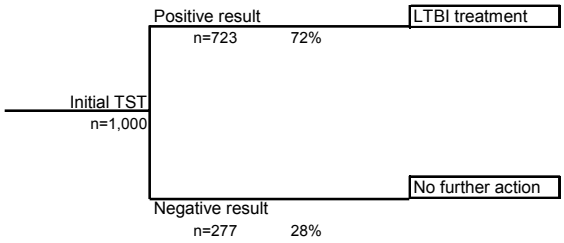
Total costs of each screening strategy		
Model 1	**Model 2**	**Model 3**
(TST only)	(T-SPOT.*TB* only)	(TST followed by T-SPOT.*TB*)
CHF 1,078,790 € 695,820	CHF 600,210 € 387,135	CHF 435,225 € 280,720

Table 3 – Overall costs of a LTBI screening and treatment program. Results expressed for a cohort of 1,000 patients. (TST cutoff 10mm)

Total costs of each screening strategy		
Model 1	**Model 2**	**Model 3**
(TST only)	(T-SPOT.*TB* only)	(TST followed by T-SPOT.*TB*)
CHF 1,078,790	CHF 600,210	CHF 435,225
Δ	CHF 478,581	CHF 643,566
no. of T-SPOT.TB tests	1000	243
incremental savings	CHF 479	CHF 2,644
overall cost neutral	**CHF 679**	**CHF 2,844**
	€ 438	**€ 1,834**

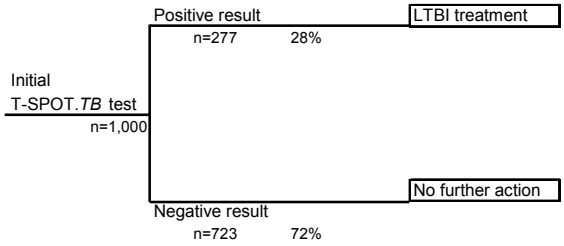
Table 4 – A simple sensitivity analysis of the cost of performing the T-SPOT.*TB* test, reporting the overall costs of the T-SPOT.*TB* test at which Model 2 and Model 3 would be cost neutral compared to the current LTBI screening guidelines using only the TST. (TST cutoff 10mm).

Model 1 - Base case
Costs of screening using the TST alone according to the Swiss guidelines (1)



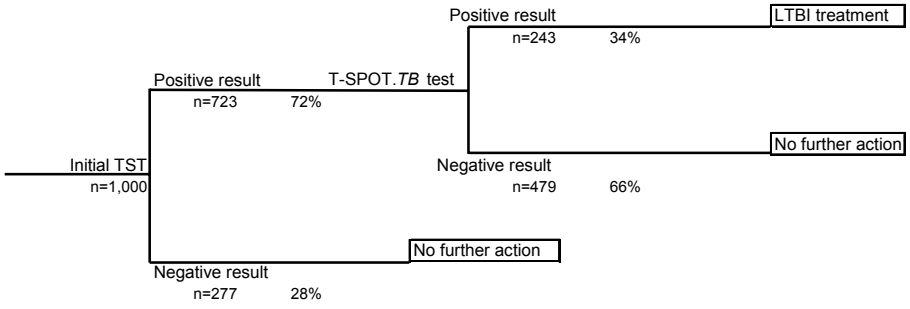
Total costs of initial screening	Total costs of treatment	**Overall total costs**
CHF 35,000	CHF 1,043,790	**CHF 1,078,790**
€ 22,575	€ 673,245	**€ 695,820**

Model 2 - T-SPOT.*TB* screening
Costs of screening if T-SPOT.*TB* were to replace TST entirely as the only tool for detecting LTBI



Total costs of initial screening	Total costs of treatment	**Overall total costs**
CHF 200,000	CHF 400,210	**CHF 600,210**
€ 129,000	€ 258,135	**€ 387,135**

Model 3 - T-SPOT.*TB* as confirmatory test
Costs of screening using TST as the first-line tool, followed by T-SPOT.*TB* in TST +ve individuals to rule out false positives



Total costs of initial screening	Total costs of confirmatory test	Total costs of treatment	**Overall total costs**
CHF 35,000	CHF 48,689	CHF 351,536	**CHF 435,225**
€ 22,575	€ 31,404	€ 226,740	**€ 280,720**

Figure 1 – The three decision-tree clinical pathway models (Models 1-3). The figure also includes the overall cost results, with data and costs normalized to a cohort size of 1,000 subjects and using a skin test cutoff of 10mm according to the Swiss guidelines

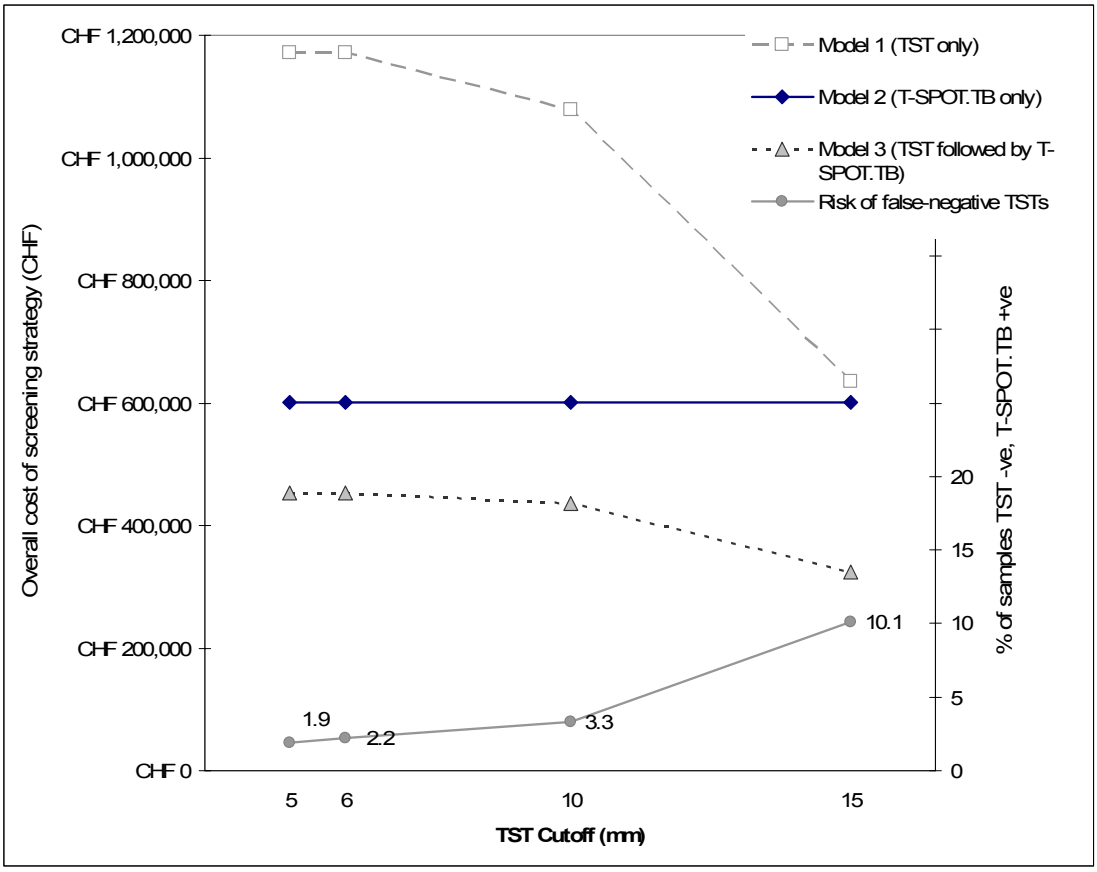


Figure 2 – The variation of the overall costs of the three screening strategies, and the risk of false-negative TST results (approximated as those samples which were TST –ve but T-SPOT.*TB* positive) with TST cut-off.