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Cost-effectiveness of IGRA testing for the treatment of latent tuberculosis in Switzerland

Short title: Cost effectiveness of IGRA testing

R. Diel[1], P. Wrighton-Smith[2], J-P. Zellweger[3]

[1]School of Public Health, University of Düsseldorf, Germany

[2]Oxford Immunotec, Oxford, UK

[3]University Medical Policlinic, Lausanne, Switzerland

Correspondence: R. Diel, School of Public Health, c/o Institute for Medical Sociology, Heinrich Heine University, Post box 101007, D-40001 Düsseldorf, Germany. E-mail: Roland.Diel@uni-duesseldorf.de. Phone: 0211/81-19776

Abstract

Objectives: To assess the cost-effectiveness of the new T-SPOT®.*TB* assay versus the Tuberculin Skin Test (TST) for screening contacts for latent tuberculosis (LTBI) in Switzerland.

Methods: Health and economic outcomes of isoniazid (INH) treatment of 20- and 40-year-old close contacts were compared in a Markov model over a 20-year period following screening with TST only (at three cut-off values), T-SPOT.*TB* alone or in combination with the TST.

Results: T-SPOT.*TB* based treatment was cost-effective at €11,621 per life-year-gained (LYG) in the younger and €23,692/LYG in the higher age group. No TST-based programs were cost-effective, except at a 15mm-cut-off in the younger group only where the cost-effectiveness (€26,451/LYG) just fell below the willingness-to-pay threshold. Combination of the TST with T-SPOT.*TB* slightly reduced the total cost compared with the T-SPOT.*TB* alone by 4.4% and 5.0% in the younger and older groups respectively. The number of contacts treated to avoid one case of tuberculosis decreased from 50 [95%CI 32-106] with the TST (10 mm cutoff) to 18 [95%CI 11-43] if T-SPOT.*TB* was used.

Conclusions: Using T-SPOT.*TB* alone or in combination with the TST for screening of close contacts before LTBI treatment is highly cost-effective in reducing the disease burden of TB.

Key Words: Cost-effectiveness, Interferon-Gamma release assay, latent tuberculosis infection, LTBI treatment, tuberculosis

Introduction

Screening contacts of patients with tuberculosis is recommended as a strategy to detect infected persons who may develop the disease at a later time. It has been demonstrated that preventive treatment, mainly with isoniazid, decreases the number of future cases of tuberculosis. This strategy is therefore recommended in countries with a low incidence rate of tuberculosis, in order to further decrease the burden of disease [1]. The effectiveness and cost-effectiveness of these programs are strongly affected by the accuracy of identifying truly infected individuals who have a risk of developing future disease. Due to the limited sensitivity and specificity of the TST, it follows that the current cost-effectiveness of screening may be improved if more accurate tools are used for screening for latent tuberculosis infection (LTBI).

Numerous studies of screening recent contacts of infectious TB patients for LTBI using the new highly-specific interferon-gamma release assays (IGRA) have recently been published [e.g. 2-7], but no study has produced cost-effectiveness data. In two papers [8,9] the way in which IGRA assays can be used for cost-saving in initial screening has been discussed. However, the long-term economic consequences and health-care outcomes of this new approach for detecting *M. tuberculosis* infection were not examined in the context of subsequent treatment of LTBI in comparison with existing programmes based upon the tuberculin skin test (TST).

As intervention options in all therapeutic areas grow, government and third-party payers, which are under increasing budgetary constraints, are seeking ways in which they can allocate resources such as to achieve maximum benefits for health care. Therefore, we conducted a cost-effectiveness analysis of several different LTBI screening strategies followed by INH treatment under a range of different conditions. In Switzerland, currently published recommendations [10] suggest the implementation of IGRAs because of their enhanced specificity over the TST as confirmatory tests for TST positive contacts, in order to minimise the number of subjects unnecessarily treated for LTBI. Therefore, the study was based on current Swiss epidemiological and cost data. As these guidelines (and the previous cost-saving analyses) only consider the increased specificity of the IGRAs; they do not take into account any healthcare gains resulting from any increased sensitivity of one or both of the IGRAs over the TST. Both because we were able to use data directly from routine clinical use of the test in Switzerland, and because the

available evidence suggests that it is the most sensitive of the two IGRAs [11,12], we chose to model the cost-effectiveness of the T-SPOT.*TB* test.

Materials and Methods

Screening strategies

Five strategies were considered: Strategies 1–3 reflect current practice, in which the TST is used as the only tool to diagnose LTBI using (i) the Swiss-standard induration cut-off (≥10mm), but also two further commonly used cut-offs (≥5 and ≥15mm); strategy 4 calculated the consequences of using the T-SPOT.*TB* alone (i.e. a complete replacement for the TST), and strategy 5 calculated the cost-effectiveness following the recommendation as described above, i.e. using the TST with a cut-off of ≥10mm for the initial screening of patients, followed by a T-SPOT.*TB* test in all TST-positive individuals before treatment.

Decision analysis model

Using the decision analysis software programme TreeAge Pro 2006 Healthcare Module, Release 0.2 (TreeAge Software Inc., Williamstown, MA) we developed a Markov model tracing the contacts' economic and health-care outcomes resulting from the test results of each strategy and two different age adult close contact groups (a young group, with a mean age of 20 years and a middle-aged group of mean age 40 years). A hypothetical cohort of 1000 individuals was used for the analysis (**Table 1b**), taken by normalising the values in **Table 1a**.

The resulting decision tree (showing in this case the T-SPOT.*TB* screening strategy) is presented in **Figure 1**. The tree is entered from the left, where the whole cohort begins at time zero as contacts. If the test results are negative, these persons are considered not to be infected, but in reality a certain proportion of them may be 'false negative', depending upon the assumed sensitivity of the test. Contacts whose results are positive go on to have a chest X-ray to exclude active TB, and are then assumed to have LTBI and offered INH treatment. It is assumed that a 9-month course of INH provides protection with an efficacy of 80% (see below) for 20 years [19] and that no re-infections with *M. tuberculosis* will occur. For modelling purposes two scenarios are followed prospectively; one where all contacts accept INH and one where none do.

The Markov model simulates the natural history of TB disease with people passing through a number of health states, defined to capture important clinical outcomes, each of which is associated with specific costs and rewards (in this case survival time). Consistent with the assumed duration of INH protection, this study used a Markov model incorporating 20 equal yearly iterations over 20 year period.

The following five mutually exclusive health states included in this model describe the various possible statuses of close contacts after they have been infected with MTB: (1) asymptomatic LTBI, (2) active illness due to reactivation, to which some of these LTBI cases progress owing to reactivation with a transition probability *tpReact*; (3) TB disease, leading to death due to the disease itself (including consequent conditions) with the transition probability *tpDcm*, or in contrast to this (4) survival after recovery without sequelae (*1 – tpDcm*); or (5) death due to "normal" all-cause mortality, excluding TB disease represented by age-dependent life expectancy, with a probability *tpDn* that is taken to affect all patients equally (i.e. whether in the LTBI or survival state).

Probabilities

Probabilities of transitions between states representing the best available data are shown in **Table 2**.

a) Risk of death

The background likelihood of dying unrelated to TB disease (*tpDn*) occurring in the general population is time-dependent, increasing with age. Data were based on the current Swiss life tables [21] and weighted according to the different life expectancies of males and females.
In Switzerland in 2004, a total of 24 of 658 persons suffering from TB died from it [22], resulting in a baseline rate of 3.7% (*tpDcm*).

b) INH efficacy

As it is described in detail elsewhere [19] we assumed that a 9-month INH course would have an 80% efficacy rate (*effect*) in preventing progression to active TB disease.

c) Risk of reactivation

The risk of TB reactivation (*tpReact*) depends largely on two risk factors: the age of the infected person and the size of induration produced by a TST. The individual risk of close contacts as recent converters were derived by the meta-analysis of Horsburgh [23] for the two age groups separated by the three induration diameters 5, 10 and 15mm. Owing to the long period of INH protection (20 years) we translated these values into a fixed transition per year (cycle) and did not take into account the increased risk of reactivation within the first two years following infection. Although we might expect that the T-SPOT.*TB* test has a higher positive predictive value than the TST for the eventual development of TB disease (see Discussion); we took the conservative assumption that the risk of TB reactivation following a positive T-SPOT.*TB* test was equal to that of the TST at a 10mm cut-off (the current Swiss standard) as a baseline value and increased it to that of the TST at 15mm in the sensitivity analysis (referred to as the "high reactivity rate").

Data inputs for T-SPOT.TB and Mantoux TST

Method-related data for this analysis were taken from a recent side-by-side comparison of the TST with T-SPOT.*TB* among 267 adult close contacts under routine programme conditions at Lausanne University Medical Polyclinic between January 2004 and December 2005. This population contained a high proportion of BCG vaccinees [9]. The TST was applied by the Mantoux method, using 2TU of RT23 PPD according to the Swiss National Guidelines [13]; results were read at 72 hours and considered positive if induration was ≥10mm and the individuals in question offered a preventive treatment with isoniazid for 9 months. For the T-SPOT.*TB,* a 10-ml blood sample was taken and analysed in a local laboratory (BBR-LTC laboratories, Lausanne); the cut-off for the assay was 6 spots, according to the manufacturer's instructions (Oxford Immunotec, UK, www.oxfordimmunotec.com).

The raw data on the results of both tests, separated by three different TST cut-offs in order to investigate the concordance between the T-SPOT.*TB* and various TST induration diameters are shown in **Table 1a**. These values were then normalised to a cohort size of 1,000 subjects (**Table 1b**) and then used to calculate inputs for the modelling.

The sensitivity and specificity for T-SPOT.*TB* were taken from the published literature. In culture-confirmed active TB patients, the sensitivity of T-SPOT.*TB* in largely immunocompetent populations has been reported between 95.4%-97.2% [11,17-18]. Higher sensitivity has also been consistently observed for the T-SPOT.*TB* assay over the TST in LTBI [2-3, 5-7] and thus a conservative baseline figure of 95% sensitivity for LTBI was taken for this analysis. The specificity of the T-SPOT.*TB* assay in low-risk healthy controls approaches 100% [14-16].

Assuming a 95% sensitivity and 100% specificity for T-SPOT.TB, it follows that there are no false-positive T-SPOT.*TB* results, but that there are 5% of truly infected people that are recorded falsely as negative. Hence if 277 subjects are recorded as positive by T-SPOT.*TB*, then there must have been 291.6 (277/0.95) subjects in the starting cohort for the analysis that are truly infected. This in turn allows the model to calculate the resulting costs and sequelae from those persons in whom a true LTBI is missed. As can be seen from **Figure 1**, the model is constructed so that the probability of a true negative result is taken directly from the negative predictive value (NPV) of the test (i.e. true negative results/total negative results). For the T-SPOT.*TB* test, the NPV can be calculated as (723-14.6)/723 = 98.0%. Likewise, the probability of a true positive result was taken from the positive predictive value (PPV) of the test, which for T-SPOT.*TB* as it is assumed to have 100% specificity (i.e. no false-positives) is 100%.

We calculated the sensitivity and specificity (and hence the NPV and PPV) for the TST relative to T-SPOT.*TB* based upon the recorded comparative data between the tests. Clearly, given the absence of a gold standard test for LTBI, we have no way of knowing which test is correct where the results are discordant. We therefore made two assumptions as described below. As T-SPOT.*TB* is assumed to have no false-positive results (100% specificity) all TST-negative, T-SPOT.*TB*-positive responses were approximated as false-negative TST results and the sensitivity of the TST calculated accordingly. There were 5, 9 and 27 individuals who were T-SPOT.*TB*-positive (**Table 1a**), but TST negative at cut-off values of 5, 10 and 15mm, indicating that the

TST test has a sensitivity, relative to the T-SPOT.*TB*, of respectively 93.2%, 87.8% and only 63.5%. The corresponding NPV for the TST are 90.7% (49/54) at a cut off of 5mm, 87.8% at a cut off of 10 (65/74) and 82.8% at a cut off of 15 mm (130/157). To calculate the PPV for the TST, we need to make an assumption of how many of the TST positive subjects are truly infected. We cannot automatically infer that only those with also a positive T-SPOT.*TB* result are infected as T-SPOT.*TB* is assumed to only have 95% sensitivity and thus will miss some individuals which may be picked up by the TST. Despite the evidence that T-SPOT.*TB* is uniformly more sensitive than the TST [2-3,5-7] we took the conservative assumption that all T-SPOT.*TB* false-negatives would be picked up by the TST. From **Table 1a**, we calculated the number of T-SPOT.*TB* false negatives as 74/0.95=77.9; 77.9-74=3.89; i.e. 4 cases rounded; and assumed these 4 were picked up by the TST. Consequently the PPV of the TST was calculated as 34.3% (73 [69+4] /213) at 5mm, 35.8% (69 [65+4]/193) at 10mm and 46.4% (51 [47+4]/110) at 15mm.

Estimation of costs

Costs are expressed in 2004 Swiss Francs (CHF) and converted to Euros where appropriate (at a rate of 1 CHF = €0.645).

Costs of LTBI screening and treatment

The costs of LTBI testing and treatment were recently published in a cost minimisation study from the Swiss health care perspective [9]. Asymptomatic infection is assumed to produce no cost (except the cost of testing, which would have been incurred irrespective of infection). The costs of testing comprised the labour cost for the staff performing the Mantoux TST or drawing blood, the material cost of the vial and associated consumables for each Mantoux TST at CHF 35 (€23). As reimbursement has not yet been formalised for the T-SPOT.*TB* test in Switzerland, an estimate for the total cost of the screening kit, reagents and laboratory fees was taken as CHF 200 (€129) for each T-SPOT.*TB* test as previously [9].

Treatment costs include an initial chest X-ray to rule out active TB prior to treatment, the costs of 9 months of INH and the costs of visits to the clinician and liver-function tests during the treatment period (see **Table 3**). Side-effects from isoniazid treatment were ignored, and all

patients for whom preventative therapy was indicated were assumed to complete the full course of therapy.

Cost of illness

The overall cost of TB disease per person was calculated from the Swiss social perspective. Thus, both direct costs for in- and out-patients (comprising also the contact-tracing induced by infectious pulmonary source cases) as the sum of the average costs for each clinical outcome weighted by the probability of occurrence of that outcome and productivity losses due to illness were included in cost estimates. The baseline cost estimates are shown in **Table 4**.

a) Epidemiological data

Of the 2485 TB cases reported in Switzerland between 2001 and 2004, 1861 (~75%), were pulmonary. Of these, 524 (28%) were sputum-smear-positive; 954 (51%) were sputum negative but culture-confirmed, and only 383 (21%) had been clinically diagnosed without bacteriological confirmation [24].

Although hospitalisation is recommended for smear-positive cases according to the current guidelines [25], only about 84% of those had been treated as in-patients in 2004, with an average stay in hospital of around 25 days; 27% of the remaining pulmonary TB cases had been hospitalised (average stay 21 days) and 16% of the non-pulmonary TB cases (average stay 10 days), for whom hospitalisation is optional (if there is co-morbidity) [individual assessment by the Swiss Federal Office of Public Health, not including long-term in-patients].

b) Direct costs

The diagnostic and treatment costs of smear-positive TB patients in 2004 amounted to CHF 39,659 per patient. Examination usually integrates three chest X-rays (at diagnosis, after 2 months and at the end of treatment) and four smear examinations (two at the start, one after 2 months, and one before the end of treatment, with strain identification and a drug sensitivity test performed on the first sample). Treatment is usually 2HRZE / 4HR, according to the WHO recommendations.

For sputum-negative patients the costs amount only to CHF 33,117 (only two sputum examinations and cultures at the start and only 21 days of hospital stay) and CHF 16,678 (10 days in hospital, only one chest X-ray examination) for the non-pulmonary cases. Before diagnosis at least two clinical visits (each 58 CHF) are necessary.

Treatment is self-administered in the majority of cases, supervised by a member or representative of the health system observing each medication intake by the TB patient (directly observed therapy, DOT) in cases with a risk of non-adherence (drug addicts, alcoholics, psychiatric cases, elderly persons with disorientation, immigrants not yet socially integrated, relapses, MDR-TB) to prevent the development of drug resistance. In 2004, 68 (11%) of the 606 Swiss TB cases were started on DOT (the percentage varying according to location, being higher in large cities than in the countryside) and remained on it for an average of four months. Of these cases, about 75% were charged CHF 10/day for administration under supervision at a dispensary 5–6 times a week, giving a monthly cost of about CHF 200 (end of treatment is usually self administered), and about 25% were given their medication by a nurse (at a house visit) 5–6 times a week, at a cost of CHF 120.-/ hour; equivalent to e. about CHF 2500/month. The average cost of DOTS normalised over the entire cohorts was therefore calculated as follows: 11% of patients receiving DOTS × average duration of DOTS × (75 % of patients under self-administration × monthly cost of self-administration *plus* 25 % of patients given nurse medication × monthly cost of nurse medication)]. Inserting the relevant values, then calculation is 0.11 × 4 × (0.75 × 200 *plus* 0.25 × 2500) = CHF341.

The costs of MDR-TB, which is rare (2% of the cases in Switzerland) and additional costs of special examinations (CT scans, biopsies) for non-pulmonary TB are not included in this listing of costs.

Contact-tracing is performed by order of the local Public Health Officer (the *Kantonsarzt*), for all cases of smear-positive pulmonary TB and in some cases of smear-negative TB if there are small children or immunocompromised persons among the contacts. In 2004, 216 contact-tracings were performed for smear-positive index cases, leading to examination of a total of 3578 persons. Therefore, one source case with at least culture confirmed TB will bring about the investigation of about 16 contacts; this will be organised by a nurse spending about one hour per contact at a

charge of CHF 120 each; giving 1920 CHF on average for every (at least culture confirmed) TB patient.

c) Indirect costs

In 2004, the average sick-leave duration of TB cases (all forms) was two months (60 days) per case [data not published]. In accordance with the *human capital approach* [26], indirect costs addressing the production loss for the economy as a whole are caused by absence from the workplace on sick leave. According to the "Hanoverian Consensus" [26], the productivity losses caused by sickness should be evaluated without consideration of differences in the nature of the work, or of differences in age or sex, with the average gross Swiss income for 2005. The average productivity loss is calculated as follows: productivity loss = number of TB-related days of work lost × [average gross income per year/365 days)] × employment rate. If the employee pay (2005: yearly average CHF 74,200 [27]) per day is multiplied by the 60 sick leave days, this results in a total of CHF 12,197.26 as the average indirect costs per adult patient. Multiplication by the employment rate for 2004 (56.2% [28]) then results in CHF 6,854.86.

Thus, the average weighted overall TB costs in CHF produced by a model patient may be calculated as follows: [(treatment cost of smear-positives × % of in-patients × % of smear-positives) + (treatment cost of smear-positives without hospitalisation × % of out-patients × % of smear-positives) + (treatment cost of smear-negatives × % of in-patients × % of smear-negatives) + (treatment cost of smear negatives without hospitalisation × % of out-patients × % of smear-negatives)] × % of pulmonary TB cases *plus* [(treatment cost for non-pulmonary TB × % of inpatients) + (treatment cost for non-pulmonary TB without hospitalisation × % of outpatients)] × % of non-pulmonary TB cases *plus* cost of visits before diagnosis *plus* DOT cost *plus* [cost for contact-tracing × % of pulmonary TB × % of culture confirmed cases] *plus* indirect costs = total costs in CHF × exchange rate to €.

Inserting the corresponding values, we calculate: [(CHF39,659 × 0.84 × 0.28) + (CHF2,584 × 0.16 × 0.28) + (CHF33,117 × 0.27 × 0.72) + (CHF2,584 × 0.73 × 0.72)] × 0.75 *plus* [(CHF16,678 × 0.16) + (CHF2,584 × 0.84)] × 0.25 *plus* CHF116 *plus* CHF341 *plus* (CHF1,920 × 0.75 × 0.79) = CHF15,734.1 *plus* CHF6,854.86 = CHF22,588.96 × 0.645 = €14,570 (rounded).

Cost effectiveness

In our model, the *incremental* cost-effectiveness ratios (ICER) of the different strategies are assessed, defined as $(C_T - C_N)$ divided by $(E_T - E_N)$, where C_T–C_N is the difference between the sum of the costs of LTBI treatment (T) minus the costs for no treatment (N) over the 20 year-period, and E_T–E_N is the difference between the effectiveness of these so-called "interventions". Effectiveness is measured in terms of the number of cases of TB disease avoided and/or the sum of saved life expectancy (generally converted to so-called "life years gained" [LYG]) to yield the net cost required to increase by one of these additional non-monetary outcome units compared with the next less costly intervention. Negative numbers thus identify cost savings (if an intervention costs less and is more effective than its comparator) while positive numbers indicate additional expenditure per outcome unit. The higher the ratio, the less cost-effective the intervention.

Quality-adjusted life-years (QALYs), the effect of interest in most other cost-effectiveness analyses, taking into account both quantity and the quality of life (and therefore affording a weight on time in different health states) have not yet been validated in any depth in connection with TB and were therefore not included in this analysis. Future costs and LYG were discounted at an annual rate of 3%.

While the question of what constitutes good value depends on ethical considerations, a rough benchmark of US $50,000 (or €40,195; average change rate for 2004: 1 USD=0.8039 Euro) per LYG has commonly been used; this is based on Medicare's decision in the 1970s to cover dialysis in patients with chronic renal failure in the United States at a cost-effectiveness ratio within this range [29]. Accordingly, we used this threshold as an indicator of willingness to pay for a health-care intervention also in Switzerland.

In addition, the total costs for each strategy is presented; broken down by treatment cost, cost due to negative test results and the contribution of costs of overlooked TB cases among false negative contacts with undetected LTBI due to the differing detection sensitivities of each strategy. The *average* cost effectiveness, defined as costs per case prevented within a given strategy, is also presented.

Sensitivity analysis

Sensitivity analyses were performed to examine the impact of uncertainty surrounding the basic model assumptions. Key parameters in this decision analysis model were varied over reasonable ranges to determine the robustness of the cost-effectiveness estimate and to determine which parameters were the most important determinants in the model. Variables explored in these analyses included the annual probability of progression to disease following a positive T-SPOT.*TB* test (with a higher risk modelled, equivalent to the rate of progression following a 15mm TST), total cost of TB treatment (with regard to possible future changes in this), and cost of INH (which accounts for about 52% of the prevention cost and is thus the greatest single cost factor). Thresholds were determined above/below which cost savings could be achieved.
Multivariate sensitivity analyses were performed on the likelihood of progression to active disease, on treatment costs for TB, and on cost of INH. The sensitivity and specificity of the TST at the different cut-offs were not changed, because these parameters are directly related to the side-by-side T-SPOT.*TB* values as conditional probabilities and cannot be evaluated in isolation.

Results

The projected clinical and economic outcomes of the different screening strategies in the two cohorts are presented in **Tables 5 and 6.**

1) 20-year-old cohort of close contacts:

1a) T-SPOT.*TB*

On the basis of T-SPOT.*TB* results, 277 contacts from the hypothetical cohort of 1000 would be deemed as infected. In the absence of any intervention, a total of 19.6 TB cases would result from these 'test-positives' over 20 years. On the basis of screening with T-SPOT.*TB* and subsequent treatment with INH, 15.6 of these cases could be prevented, saving 10.3 days of life (or 0.0283 life-years) per treated contact and costs of disease amounting to €227,292 (15.6×€14,570). Assuming a sensitivity of only 0.95 for T-SPOT.*TB* in the base-case, one additional case of TB would have resulted from unrecognised false negative results.

For the high-reactivation probability scenario (i.e. assuming the same reactivation probability for T-SPOT.*TB* as that from a ≥15mm TST result), 29.2 cases would occur and 23.1 of them would be prevented by INH treatment, and 1.5 cases would be missed from false-negatives We also calculated the effectiveness of the screening strategies on the basis of the number of contacts treated to prevent one active TB case; this was calculated as 18 contacts treated/case prevented [95%CI 11–43] for a normal reactivation probability and 12 [95%CI 7–59] for a high reactivation probability with the T-SPOT.*TB* test.

Turning to the costs; under base-case assumptions, €104,432 of a total of €441,310 (23.7%) are expended upon negative results comprising the costs of the 723 negative T-SPOT.*TB* screening tests and €12,836 upon the consequences of false negative results (2.9%). The incremental cost-effectiveness comparing LTBI treatment versus non-treatment is therefore €11,621/LYG, rapidly improving to only €854/LYG when the high-reactivation probability is used; the cost per case prevented is €28,289 and €20,288 respectively.

Reducing the cost of INH medication in sensitivity analysis to €154 (i.e. levels more comparable with the rest of Europe) would result in an overall cost saving (negative ICER) with T-SPOT.*TB* when LTBI treatment is offered. This would also be the case if the costs resulting from TB disease were above €22,463.

Assuming the high-reactivation probability, even a very small decrease in INH cost to €448 (i.e., by about 7%) would be enough to make T-SPOT.*TB* cost-saving overall as would only a modest increase of 3.7% in assumed cost of TB disease (from €14,570 to €15,112).

1b) TST ≥5mm

Performing the TST with a cut-off at 5mm resulted in a total of 798 test positives, 2.88 times as many as obtained by T-SPOT.*TB,* resulting in a large number (525 [798-273]) of contacts assumed to be offered INH unnecessarily. Although the combination of low number of test negative persons on one hand and high negative predictive value (0.907, see above) resulted only in slightly more than one case (1.1) being missed, on the other hand the treatment cost are more than double (2.4-times) the comparable T-SPOT.*TB* costs. Thus, the ICER is €96,705/LYG is

more than 8 times higher than with the T-SPOT.*TB*. The only way this screening strategy could be considered cost-effective under the normal willingness-to-pay threshold is if INH medication could be offered without charge. In that case the ICER would fall to €35,707/LYG. Cost savings would be achieved only with unrealistically high TB costs of €80,445 or higher. 63 contacts [95%CI 40-158] have to be treated to prevent one TB case and the cost per active TB case prevented is €64,455.

1c) TST ≥10mm

A cut-off at 10mm for the TST does not substantially reduce treatment costs or ICER, as here too the ratio between the false-positives (465 [723-258]) to true-positive contacts 258 remains high at 1.8. Total treatment cost are only 6.1% lower, but the costs due to false negative results are more than two times (2.17) higher because of the lower negative predictive value of the TST at a 10-mm compared to a 5-mm cut-off. These false-negatives result in 2.4 missed cases. A reduction of the INH price to €171 or an increase in TB cost to €35,600 (data not shown) would make this strategy cost-effective at the €40,195/LYG threshold, and cost-savings are only apparent if the costs of treating TB would be €62,982. 50 contacts [95%CI 32-106] have to be treated to prevent one TB case and the cost per active TB case prevented is €52,229.

1d) TST ≥15mm

Using the cut-off at 15mm clearly reduces the number of TST-positive individuals (412 instead of 723 as for the 10mm cut-off) and further decreases the proportion of unnecessarily treated individuals ([412-191]/412=53.6% instead of [723-258]/723=64.3%). Due to higher positive predictive value than for 5 and 10mm cut-offs, and the high reactivation probability of 0.0056 a year, the ICER for this base case is the only TST screening strategy that falls below the willingness-to-pay threshold with an ICER of €26,451/LYG. Nevertheless, the low negative predictive value leads to a high number of missed cases (10.7) and therefore additional costs of €127,662 due to false negative results, i.e. nearly one quarter (22.6%) of the total costs. Furthermore, reducing the INH medication price to zero would only diminish the ICER to €1,800 /LYG; a cost saving can only be achieved if at the same time the TB treatment cost rises to

€15,799; an increase of about 8 %. 26 contacts [95%CI 19-42] have to be treated to prevent one TB case and the cost per active TB case prevented is €35,589.

1e) TST ≥10mm followed by T-SPOT.*TB*

The introduction of screening first by TST with a cut-off at 10mm and followed by the T-SPOT.*TB* as a confirmation test has no impact on the ICER compared with the T-SPOT.*TB* alone, but it does falsely reduce the number of treated contacts presumed to be infected by 9.3 % (258 versus 277) after preselection by the TST. The resulting lower treatment costs (€17,938 less) just outweigh the higher costs induced by the higher number of false-negative contacts (€26,416 compared with €12,836 for the performance of the T-SPOT.*TB* test alone). However, due to the lower number of treated contacts and subsequently lower number of cases avoided, the combination slightly increases the cost per case avoided by about €597 (2.1%), leading to a marginally worse average cost effectiveness than the T-SPOT.*TB* alone. The number of contacts needed to treat to avoid one future case of tuberculosis is unchanged: 18 [CI 95% 11-43].

2) 40-year-old cohort of contacts

The risk of disease in those who were infected is lower in elderly LTBI patients, and therefore the sum of the future cost of TB will be relatively low in comparison with those for the 20-year-old contacts, because of the lower number of cases of active TB disease. As expenditures for LTBI treatment remain constant, the ICER will (in contrast to the 20-year-old group) rise rapidly in all strategies applied to the 40-year-old contacts. Only the T-SPOT.*TB*-based treatment under base-case estimates, and even more under the high-progression probability assumption, is cost-effective, achieving an ICER of €23,692/LYG and €8,642/LYG respectively. Cost savings can be achieved if the INH costs decline to €6 and €225 per treatment course under base-case and the high-progression probability assumptions, respectively. None of the TST strategies without combination with the T-SPOT.*TB* are cost-effective under any reasonable combination of other parameters.

Discussion

Until recently, cost-effectiveness analyses of LTBI treatment were based on outdated assumptions regarding sensitivity and specificity derived from TST parameters. Mostly varying between 95% and 99% [e.g. 16, 25, 26], they could not take account the results of new scientific discoveries showing the lack of specificity of the TST, and may for this reason lead to a systematic bias by overestimating the number of contacts potentially infected and therefore the number of cases prevented as the numerator of the incremental cost-effectiveness ratio. In this work, we set out to assess the consequences for cost-effectiveness of screening and treating LTBI patients in Switzerland on the basis of current "real life" results in a comparative LTBI screening study that compared the new T-SPOT.*TB* assay and TST-based strategies among close contacts of infectious pulmonary TB source cases. An inherent limitation of this, and indeed any, analysis designed to compare cost-effectiveness against an imperfect standard (such as the TST) is that we do not have a gold standard test to be able to consult in order to separate discordant results. We are forced to make various assumptions as to which test result is more likely to be the correct one as the basis of generating quantitative comparative performance measures. This limitation should be recognised in interpreting the results.

Although is not imperative that the implementation of a programme for preventing infectious diseases result in monetary savings to be cost-effective it cannot be assumed that societies are willing to pay any price for preventive interventions. Therefore any new intervention must have an acceptable cost associated with the health benefits it brings.

In the 20-year-old close contacts the baseline strategy of screening combining the TST at a cut-off of 10mm and subsequently the T-SPOT.*TB* was the least costly alternative; however, the most cost-effective on average was the use of T-SPOT.*TB* alone. Referred to the threshold of $50,000 (or €40,195) per life year gained, no TST-based programs were cost-effective; with the exception of using a 15mm-cut-off in the younger group where the cost-effectiveness (at €26,451/LYG) fell below the willingness-to-pay threshold. However, this came at the price of producing the highest total cost due to low sensitivity and therefore an unacceptably high rate of missed MTB-infected contacts developing TB disease in the future. Using the T-SPOT.*TB* test, either alone or in combination with the TST, greatly reduced the number of people it was necessary to treat in order to prevent one TB case (from 50 to 18) versus the *status quo* of TST cutoff ≥10mm.

The sensitivity analysis showed that the cost of the INH medication for the 9 month-course (currently €482 in Switzerland) appeared to be the most important cost parameter. For example, if the cost of INH was assumed to be reduced by 2/3rds then the two T-SPOT.*TB*-based strategies become cost-saving; that is, saving both total costs and life-years. This is important for the generalisation of the results to other countries as the cost of INH appears to be much higher in Switzerland than elsewhere (for example, the cost of 9 months of INH in Germany is €70.20 [19]) particularly where generic drugs are used.

The risk of progression to active disease after LTBI in the 40-year-old cohort of contact individuals appeared to have the greatest influence on the cost-effectiveness outcome. Whilst reasonably reducing cost of INH medication would not result in considerable changes in the cost-effectiveness owing to the comparatively low annual reactivation base-case probabilities inherent in older infected persons, the high-progression assumption led to a low ICER for using the T-SPOT.*TB* and, combined with a moderate INH price decrease in the sensitivity analysis, even to a cost reduction. This has important implications when we consider the applicability of these findings to the screening of groups at particularly high rates of reactivation, such as HIV-infected patients in both low and high prevalence settings.

Given the importance of the assumed rate of progression to active TB as a variable in the model, it deserves further discussion. In particular, as we do not yet have long-term prospective follow-up studies showing the risk of developing active TB following a positive blood test (except for one small study [30]), the reactivation probability for T-SPOT.*TB* positive individuals is still unknown and this limits the accuracy of this analysis. In the absence of any other data, we assumed that this value for T-SPOT.*TB* was comparable to that for the TST, using values from a recent meta-analysis [23]. However, this assumption is likely to underestimate the true cost-effectiveness of T-SPOT.*TB* as its greater sensitivity and specificity should result in a higher positive predictive value than found with the TST. This is because in prospective studies with the TST where the reactivation rate is calculated as from the incidence of active TB disease deriving from a certain number of TST positive individuals, a proportion of the followed-up TST positives will never have been TB infected due to the known false-positive results induced by both prior BCG vaccination and non-tuberculous mycobacterial infection. This systematic error serves to underestimate the true risk of reactivation in those who were genuinely infected. At the same time, the TST is known to suffer from false-negative results, and these occur disproportionately

in those with weaker immune systems. These people are ironically also those who are greatest risk of reactivation. By excluding these truly-infected individuals who were negative to the TST from the subsequent follow-up, the true reactivation rate of those truly infected is again underestimated. Using a test that has higher sensitivity (identifying more of those are high risk of reactivation) and higher specificity (not identifying uninfected patients) than the TST, the subjects found to be positive can thus be reasonably assumed to have a higher reactivation rate than the TST. If T-SPOT.*TB* does indeed demonstrate a better positive predictive value for the subsequent development of TB disease than is currently observed with the TST, then the cost-effectiveness of T-SPOT.*TB*-based screening will be dramatically increased from that modelled here. This is an important area for future study.

The possible benefits of the T-SPOT.*TB* assay are also underestimated due to the fact that our model did not include wider transmission of TB into the community (i.e. the active TB cases that occur themselves infecting new contacts) over the 20 years. Adding these to the decision tree would certainly increase the benefits from INH treatment, but it would also make this model even more complex.

Despite these limitations, we believe this study has four important outcomes. Firstly it illustrates that the historical solely TST-based screening strategies and preventive treatment of LTBI are arguably not cost-effective medical interventions when set against a benchmark of €40,195/LYG. Secondly, the findings of this study show that using T-SPOT.*TB*-based screening are cost-effective (taking the same measure) in an absolute sense and will be net cost-saving if INH costs are close to international norms. Thirdly, T-SPOT.*TB*-based screening strategies are significantly cost-saving when compared to the status quo of TST-based TB control programs. Lastly, the use of T-SPOT.*TB* (either alone or in combination with the TST) greatly reduces the number of contacts treated to prevent one TB case, from 26-63 (depending the cut-off for positive TST) to 18.

Reducing the number of persons needing to be treated to avoid one case of tuberculosis by a better selection of infected contacts may have important implications in countries with a low incidence of tuberculosis as an addition to the global elimination strategies. In high-prevalence

countries, particularly in regions where the rate of latent tuberculosis infection among HIV-positive patients is elevated, and considering the fact that the T-SPOT.*TB* test appears more sensitive and more specific than TST in advanced immunosuppression, such a strategy could also be considered as a possible way to reduce the burden of disease and the costs associated with reactivation of tuberculosis by offering preventive treatment to infected patients [31-36].

These findings have important ramifications for healthcare providers in setting new guidelines for the use of this new test, and underline the validity of the new Swiss screening recommendations.

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Table 1a: Raw results of TST- and T-SPOT.*TB* testing in a population of 267 close contacts, separated by cut-off of induration diameter

T-SPOT.*TB* result	TST (≥5 mm)		total
	negative	positive	
negative	49	144	193
positive	5	69	74
total	54	213	267

T-SPOT.*TB* result	TST (≥10 mm)		total
	negative	positive	
negative	65	128	193
positive	9	65	74
total	74	193	267

T-SPOT.*TB* result	TST (≥15 mm)		total
	negative	positive	
negative	130	63	193
positive	27	47	74
total	157	110	267

Table 1b: Results after scaling to 1000 (rounded)

T-Spot.*TB* result	TST (≥5 mm)		total
	negative	positive	
Negative	184	539	723
Positive	18	258	277
Total	202	798	1000

T-SPOT.*TB* result	TST (≥10 mm)		total
	negative	positive	
negative	243	479	723
positive	34	243	277
total	277	723	1000

T-SPOT.*TB* result	TST (≥15 mm)		total
	negative	positive	
negative	487	236	723
positive	101	176	277
total	588	412	1000

Table 2: Base-case estimates used in cost-effectiveness analysis

Variables			20-(40-)year-old cohort	Reference
Demographic variables				
Age [years]			20 (40)	–
Prophylaxis variables				
Efficacy of complete (9-month) course of isoniazid (annual reduction in probability of developing TB), [effect]			0.8	[16]
Methodological variables				
TST	relative sensitivity	≥ 5mm	0.932	[modified from 9]
		≥ 10mm	0.878	
		≥ 15mm	0.635	
	PPV	≥ 5mm	0.343	
		≥ 10mm	0.358	
		≥ 15mm	0.464	
TST	NPV	≥ 5mm	0.907	
		≥ 10mm	0.878	
		≥ 15mm	0.828	
T-SPOT.*TB*	sensitivity		0.95 (range 0.92–0.97)	[14,15]
	specifity		1.0	[11,12,13]
Tuberculosis variables				
Annual probability of TB disease with no isoniazid [tpReact], dependent on TST induration size			in 16–35 (36–55)-year-old converters	[19]
5–9 mm			0.0030 (0.0023)	
10–14mm			0.0037 (0.0028)	
≥ 15 mm			0.0056 (0.0042)	
T-SPOT.*TB*			0.037–0.0056 (0.0028–0.0042)	Assumption
Annual probability of death given occurence of TB [tpDcm]			0.037	[18]
Annual all-cause probability of death [tpDn]			see Swiss life tables	[17]
Costs, €				
per course of isoniazid (daily for 9 months)			482	[7]
per case of tuberculosis			14,570	Model estimation
Discount rate, %			3	–

TB: tuberculosis; TST: Tuberculin Skin Test; PPV: positive predictive value

Table 3. Costs of preventive therapy (LTBI), consisting in 9 months of isoniazid, in CHF, assuming there is no side-effects or additional examination:

10 clinical visits (58 CHF each)	580.-
1 chest X-ray (to rule out active TB)	63.-
3 liver function tests (average) at 18 CHF	54.-
Isoniazid for 9 months	747.-
Total	1,444.-
	(€931.-)

Table 4. Costs of treatment of smear-positive pulmonary TB according to the current Swiss guidelines, in CHF, assuming a hospital stay of 25 days, no side-effects, no interruption of treatment and monthly controls after the hospital stay:

Hospital stay (25 days at 1483.-)	37,075.-
6 clinical visits (58.-)	348.-
3 chest X-rays (63.-)	189.-
6 sputum examinations (start, 2 months, end)	
4 direct smears and cultures (150.-)	600.-
1 identification	150.-
1 sensitivity testing	160.-
3 liver function tests	54.-
Rifater (HRZ) 5 Tab/day for 60 days	400.-
Ethambutol 1200 mg/day for 60 days	168.-
Rifinah (HR) 3 Tab/day for 120 days	515.-
Total:	39,659.-
	(€26,439.-)

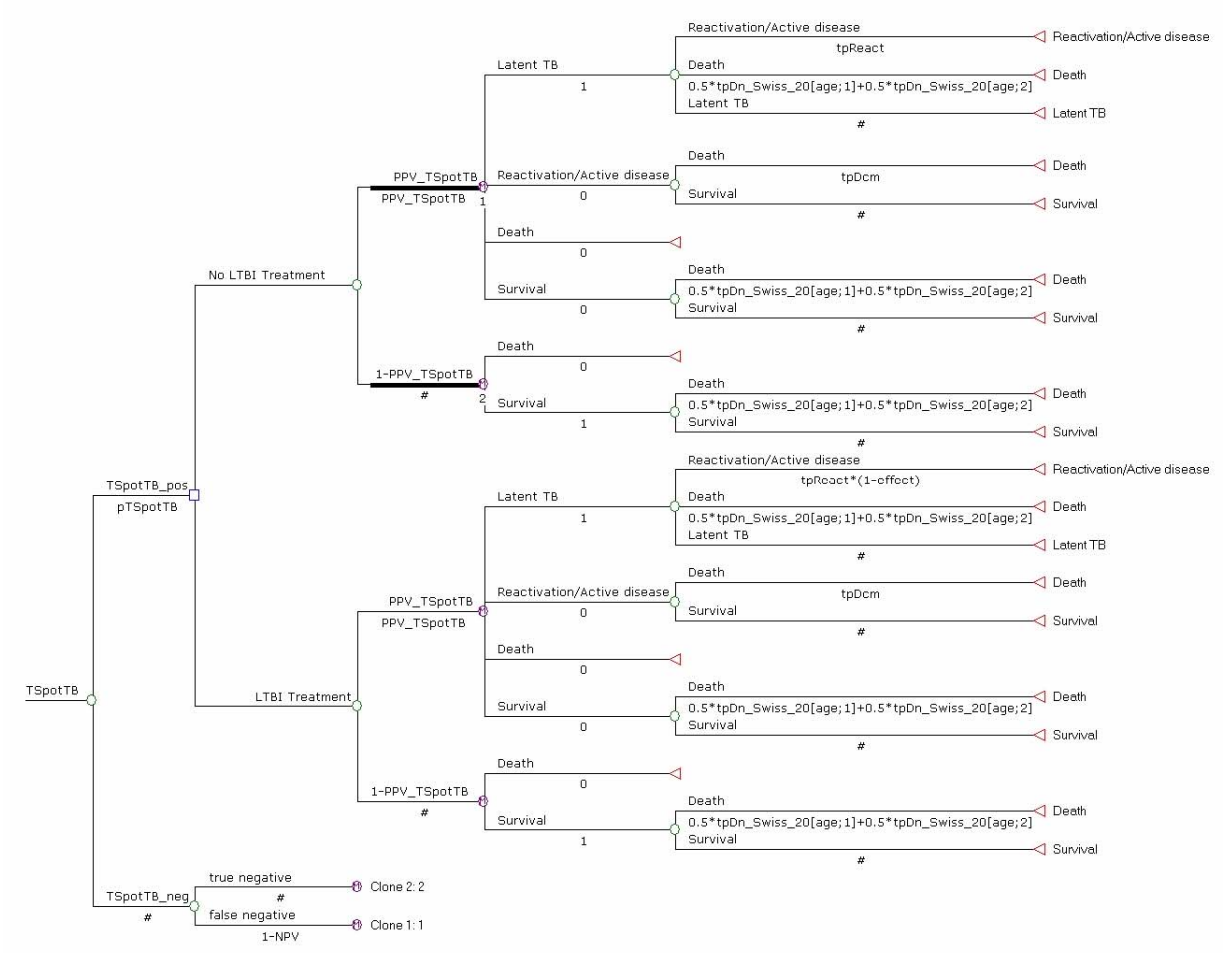

Figure legend: Markov model for predicting the total costs and the occurrence of tuberculosis (TB) due to latent TB by screening a cohort of 20 year-old close contacts and treating the test-positives with INH using the T-SPOT.*TB* strategy. A decision node (□) is the decision after a positive T-SPOT.*TB* test to accept isoniazid (INH) or not. Branches from a change node (o) represent the possible outcomes of an event; branches from a markov node (M) represent the possible different health states. A terminal node (◁) represents a state from which an individual will jump to the next cycle. Only the state death is an absorbing one and cannot be departed from. The bold horizontal lines indicate that the following subtree is cloned, i.e. a copy is attached to a node in another branch of the tree. The cloned subtrees, denoted 1 and 2, are attached to the false negative- and the true negative-node, respectively.

Probabilities (p) are as follows: pTSpotTB: probability of T-SPOT.*TB* being positive; tpReact: transition probability for a progression to active TB; tpDn_20: probability of death due to causes

other than TB among contacts with an initial age of 20; tpDcm: probability of death due to TB. #: complementary probability (all probabilities of chance node's branches to sum to 1.0). NPV: negative predictive value; PPV: positive predictive value. Effect: Efficacy of INH to prevent progression to manifest TB in per cent.

Table 5: Health and economic outcomes: 20-year-old cohort

	Screening Strategy				
Model Outcomes	**T-SPOT.*TB***	**TST ≥ 5mm**	**TST ≥ 10mm**	**TST ≥ 15 mm**	**TST ≥ 10/T-SPOT.*TB***
Number of persons tested positive	277	798	723	412	initially 723
Numbers of test-positive persons carrying LTBI	277	273	258	191	258
Numbers of TB cases predicted in test positives in absence of intervention	19.6	15.8	18.3	20.1	18.3
Active cases averted by treatment	15.6	12.6	14.6	15.9	14.6
Active cases missed from false negatives	1.0	1.1	2.4	10.7	2.4
Base Assumptions					
Total cost, for 1000 contacts (treated), Euro	441,310	812,134	762,538	565,873	421,742
-due to treatment	336,968	795,740	730,599	438,211	319,030
-due to negative results	104,432	16,394	31,939	127,662	102,712
--due to false negative results	12,836	12,185	26,416	116,663	26,416
Incremental cost-effectiveness ratio (ICER)	11,621/LYG	96,705/LYG	70,955/LYG	26,451/LYG	11,621/LYG
Cost per active TB case prevented, Euro	28,289	64,455	52,229	35,589	28,886
Average increased life expectancy (LY) per patient from INH treatment (days)	10.3 (0.0283yr)	2.9 (0.00789yr)	3.7 (0.0101yr)	7.2 (0.0196yr)	10.3 (0.0283yr)
Number needed to treat to prevent one TB case	18 [11-43, CI 95%]	63 [40-158, CI 95%]	50 [32-106, CI95%]	26 [19-42, CI 95%]	18 [11-43, CI 95%]
Thresholds for overall costs-savings					
If total TB treatment costs increase to Euro (+/- amount of change)	22,463 (+7,893)	80,445 (+65,875)	62,982 (+48,412)	32,681 (+18,111)	22,463 (+7,893)
if INH costs decrease to Euro (+/- amount of change)	154 (-328)	-	-	-	154 (-328)

***Higher* T-SPOT.*TB* reactivation rate assumption** *(tp React 0.056)*					
Absolute numbers of TB cases predicted in absence of intervention	29.2				
Active cases averted by treatment	23.1				
Active cases missed from false negatives	1.5				
Total cost, for 1000 contacts (treated), Euro	468,651				
-due to treatment	358,881				
-due to negative results	109,770				
--due to false negative results	18,213				
ICER	854/LYG				
Cost per active TB case prevented, Euro	20,288				
Average increased life expectancy (LY) per patient from INH treatment (days)	15.4 (0.0422yr)				
Number needed to treat to prevent one TB case	12 [7-59, CI 95%]				
Thresholds for overall costs-savings					
If total TB treatment costs increase to Euro (+/- amount of change)	15,112 (+542)				
if INH costs decrease to Euro (+/- amount of change)	448 (-34)				

Table 6: Health and economic outcomes: 40-year-old cohort

	Screening Strategy				
Model Outcomes	**T-SPOT.*TB***	**TST ≥ 5mm**	**TST ≥ 10mm**	**TST ≥ 15 mm**	**TST ≥ 10/T-SPOT.*TB***
Number of persons tested positive	277	798	723	412	initially 723

Numbers of test-positive persons carrying LTBI	277	273	258	191	258
Numbers of TB cases predicted amongst test-positives in absence of intervention	14.8	12.0	13.8	15.1	13.8
Active cases averted by treatment	11.8	9.6	11.0	12	11.0
Active cases missed from false negatives	0.77	0.84	1.8	8	1.8
Base Assumptions					
Total cost, for 1000 contacts (treated), Euro	427,792	801,041	746,191	525,889	406,334
-due to treatment	326,176	787,437	720,543	426,726	309,870
-due to negative results	101,616	13,604	25,648	99,163	96,464
--due to false negative results	10,137	9,395	20,108	88,115	20,261
Incremental cost-effectiveness ratio (ICER)	23,692/LYG	141,502/LYG	107,151/LYG	44,831/LYG	23,692/LYG
Cost per active TB case prevented , Euro	28,905	83,442	67,836	43,824	36,939
Average increased life expectancy (LY) per patient from INH treatment (days)	7.3 (0.0201yr)	2.1 (0.00567yr)	2.6 (0.00718yr)	5.0 (0.0138yr)	7.3 (0.0201yr)
Number needed to treat to prevent one TB case	24 [14-75, CI 95%]	83 [49-268, CI 95%]	66 [41-171,CI95%]	34 [24-61, CI 95%]	24 [14-75, CI 95%]
Thresholds for overall costs-savings					
If total TB treatment costs increase to (Euro) (+/- amount of change)	29,759 (+ 15,189)	105,401 (+ 90,831)	83,404 (+68,834)	43,442 (+28,872)	29,759 (+15,189)
if INH costs decrease to (Euro) (+/- amount of change)	6.01 (-475.99)				6.01 (-475.99)
Higher* T-SPOT.*TB reactivation rate assumption *(tp React 0.0042)*					
Absolute numbers of TB cases predicted in absence of intervention	21.9				

Active cases averted by treatment	17.4				
Active cases missed from false negatives	1.3				
Total cost, for 1000 contacts (treated), Euro	447,852				
-due to treatment	342,202				
-due to negative results	105,650				
--due to false negative results	14,131				
ICER	8,642/LYG				
Cost per active TB case prevented, Euro	25,739				
Average increased life expectancy (LY) per patient from INH treatment (days)	10.9 (0.0299yr)				
Number needed to treat to prevent one TB case	16 [10-36, CI 95%]				
Thresholds for overall costs-savings					
If total TB treatment costs increase to (Euro) (+/- amount of change)	20,194 (+5,624)		-	-	-
if INH costs decrease to (Euro) (+/- amount of change)	225 (-257)		-	-	-