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Cost optimization of screening for latent tuberculosis in close contacts

Short title: cost optimization of LTBI screening

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Abstract

Objectives

To perform a cost-minimisation analysis of contact investigation from a Public Health perspective by using the tuberculin skin test (TST) and a new blood assay, QuantiFERON-TB Gold (QFT-G).

Methods

A decision-analysis model simulated the costs of investigating a cohort of adult close TB contacts by the Public Health Service following the current German guidelines over a period of two years. The economic outcomes were compared with alternative screening strategies. These were: (i) QFT-G instead of TST, (ii) TST followed by QFT-G, and (iii) TST followed by QFT-G in BCG-vaccinated subjects.

Results

In a base-case analysis, the costs of TST-based screening were € 91.06 per contact, assuming a 1% TB case-finding incidence. The least expensive strategy was TST screening plus subsequent QFT-G testing (€ 52.05) resulting in a 43% cost reduction. Using QFT-G only in BCG-vaccinated subjects who tested positive in the TST led to a 39% cost reduction. The savings by using QFT-G alone instead of TST amounted to € 29.77 per contact. The results depended on the acquisition costs assumed and the proportion of positive results in TST-based screening.

Conclusions

Screening for TB by combining TST and QFT-G markedly reduces Public Health costs compared with TST screening only.

Keywords**:** cost, cost-minimisation analysis, latent tuberculosis, contact investigation

Introduction

Although routine contact investigation of infectious tuberculosis (TB) cases is a key component of TB-control programs in most countries, only few studies have addressed the costs to the Public Health agencies that usually perform this most important task [1,2] and which are financed by the local municipalities through tax revenues.

Contact investigation is based on the established fact that individuals recently infected with *Mycobacterium tuberculosis* (MTB) are at greatest risk of developing the disease shortly after becoming infected. The lifetime risk of TB reactivation largely depends on the age of the infected person and the size of induration produced by a tuberculin skin test (TST) varying between 8%, 10% and 13% respectively among adults 16–25 years of age in three categories of skin-test reactions (induration of at least 5, 10 and 15 mm); the corresponding risk is 4%, 5% and 7% among adults 35–45 years of age [3]. However, an estimated 50% of the latent tuberculosis (LTBI) cases that will ever develop active disease do so within the first two years following infection [4].

There are two courses the Public Health Service can take if the TST result in a contact person is positive. These are complementary and serve the goal of preventing the spread of disease to the general public thus breaking the chain of infection.

The first is to offer an isoniazid (INH)-chemoprevention to contact persons suspected of having LTBI. The second approach – for contact persons who do not or cannot accept the offer of treatment – entails the screening for active TB disease through a series of subsequent X-ray examinations that covers the 2-year observation period. In different countries the national recommendations focus on different points. Whilst the recently published US recommendations of the Centers for Disease Control and Prevention (CDC) [5] emphasize chemoprevention and only provide for an initial chest X-ray to exclude active pulmonary TB infection, the British recommendations [6] call for follow-up X-ray examinations 3 and 12 months after the initial

examination of contact persons who decline chemoprevention. In such cases, the German recommendations call for X-ray follow-up after 3, 9, and even after 15 months [7] (see Figure 1).

Administration of INH (300 mg for 9 months recommended in Germany [8]) to recent converters by practicing pneumologists who follow these patients has been clearly proven to be cost-effective [9]. The costs of medication and observation by the physician until the end of the prevention therapy, however, are paid by the German statutory health insurance organisations called the "Public *Krankenkassen,* and, thus, lie beyond the economic scope of Public Health Service and this study. Of concern, however, to the Public Health Service is the eventual neglect of its other obligatory and legal duties in connection with TB. The active seeking out and care of persons at risk for TB disease (particularly the homeless) competes with contact tracing activities for scarce resources. It is therefore imperative, that contact investigation be carried out as efficiently as possible.

As an alternative to the TST for LTBI screening, MTB-specific gamma-interferon (IFN-γ) assays have recently become available. These claim not only a higher specificity regarding the degree of exposure of contacts to the source case, but also missing or limited cross-reactivity in those vaccinated against *M. bovis* BCG or infected by non-tuberculous mycobacteria (NTM) [e.g.10-14]. One important aspect of the differences between the TST and the INF-γ tests is that their different results lead to different numbers of subsequent contact investigation procedures (X-ray or INH-chemoprevention).

Against the background of increasingly limited resources, we sought to assess the costs of screening contacts for MTB infection (including repeated Chest X-ray for surveillance) and to conduct a cost-minimisation analysis within the framework of the German Public Health System, taking as an example the city of Hamburg. Hamburg is one of the German federal states and, with 1.73 million

residents, the second largest city in Germany; in 2004 it had the highest TB incidence rate (12.0 per 100,000) of all the federal states.

In the absence of a "gold standard" reference test for LTBI, it is impossible to compare directly the accuracy (sensitivity and specificity) of the two assays, the effects of BCG vaccination on each test, and thus the relative medical benefit of each testing strategy. Others have addressed these questions in different groups [13,14]. Therefore, in contrast to Markov modeling, the decision-tree analysis we use ignores the dynamics of progression to disease by following a cohort for decades. It only takes account of the costs which would immediately be incurred upon following the screening steps

The cost-minimisation analysis, applied when the consequences of the alternatives are deemed to be equal, is a special type of cost-effectiveness analysis that aims to achieve a given goal of prevention at a lower cost. Unlike the dynamic development of a TB illness over the entire lifetime of a single MTB-infected individual in western industrial countries, the percentage of contact individuals who have fallen ill within the short period of 2 years since detection of a particular TB-case has – independent of the year studied and population observed – proven to be relatively stable at 1% to 2% in a large cohort of contact persons [15-18].

In this context, the more cost-effective intervention is defined in terms of testing cost alone. In doing this, we attempted to follow the current German guidelines and also to take account new options as proposed in the national recommendations of other western countries.

Methods

Screening strategies and input of relative probabilities

Recent CDC recommendations [5] suggest, that the whole blood IFN-γ test QFT-G can be used in contact investigations to replace, and not to supplement, the TST; and the results of QFT-G should prompt the same evaluation and management as the TST. However, because the greater correlation

of QFT-G with exposure, and enhanced specificity over the TST, it may be a reasonable option to use this test as a confirmatory test for those TST positive and therefore minimise the number of subjects evaluated for active TB (i.e. chest X-ray and possibly treated for LTBI). This procedure is currently suggested in the Swiss recommendations [19] and the draft NICE guidelines for the National Health Service in England and Wales [20]. Such a procedure may be additionally beneficial when screening BCG-vaccinated contacts in routine contact investigation, where false-positive TST responses would be more commonly expected [12]. In addition, QFT-G excludes false positive TST results due not only to BCG but also due to boosting (if repeated for any reason) and non-tuberculous mycobacteria [13,14].

Recently, in a prospective "real world" comparison study regarding routine contact investigation of close contacts containing a high proportion of BCG-vaccinated persons, we assessed the results from 309 contacts (aged 28.5 ± 10.5 years) of 17 index cases simultaneously tested by both QFT-G and the TST in the period between May 1, 2005 and October 31, 2005 (see Table 1). Of those, 157 (50.8%) had received BCG vaccination and 84 (27.2%) had migrated to Germany from a total of 25 different countries. For the TST, the positive response rate was 44.3% (137/309), whilst only 31 (10%) showed a positive QFT-G result. These results are consistent with those of two recent contact tracing studies where TST results were strongly associated with prior BCG vaccination and more than 80% of the TST-positive, BCG vaccinated contacts did not respond to ESAT-6 in IFN-γ ELISPOT tests [21,22].

"Close" contacts were defined as household and intimate contacts (these also comprised employees who had demonstrable continuous exposure to the source case, or pupils sharing the same classroom) whose aggregate exposure time was not less than 40 hours within the period of infectiousness [18]. TST results were considered positive if induration was > 5 mm according to the current German guidelines [7], which, in line with the CDC guidelines, disregard BCG vaccination status in order to provide maximum sensitivity.

Using the frequencies for test results and other parameters obtained from this prior study we were able to compare the expected costs (in Euro) of four optional strategies within the context of a contact investigation program. The strategies compared were as follows:

1. TST,
2. QFT-G alone,
3. TST followed by QFT-G for contact persons with a positive TST, and
4. TST followed by QFT-G only for previously BCG-vaccinated contacts with a positive TST.

Decision analysis model

To perform the cost-minimisation analysis, a decision-tree model was developed to trace the economic outcomes for a hypothetical cohort of 1000 adult close contacts of patients with sputum-smear positive pulmonary TB (see Figure 2). The whole cohort begins at time zero in the contact state, entering the tree from the left. The model is evaluated by attaching probabilities to each branch of the tree and rewards (component costs that are used to calculate total cost for each scenario) to the terminal nodes on the right. The calculation of costs includes not only the first chest X-ray, but also the two subsequent X-ray examinations. Decision-analytical calculations were performed with TreeAge Pro Healthcare Module 2005 (TreeAge Software Inc.,Williamstown, Massachusetts, U.S.A.).

As stated above, four possible testing strategies were compared:

1) TST

We assume that a TST is administered to the entire cohort, but that there is a small proportion of contacts (4.8% of all contacts tested in our Public Health Department in 2004, see below) who will not return to have the result read (1-*pRead*). All other contacts represent the final fraction having a

TST result. For simplicity, we assume that no patient requires a second test. No further action will be taken with contacts showing negative TST results. Contacts exhibiting a positive skin reaction (*pTST*) will be requested to undertake chest X-ray examination. Once active TB has been excluded, these people are assumed to be cases of LTBI and may be offered INH-chemoprevention (*pPrev*). Those who do not receive INH (1- *pPrev*) will be further examined by undergoing a second and third chest X-ray examination at the aforementioned time intervals. The contact investigation will end after this if X-ray examinations do not indicate a pulmonary TB. Any contact suspected of having pulmonary TB will be referred for further diagnosis to an outpatient pulmologist or chest clinic (*pTB*).

2) QFT-G

By completely replacing the TST with QFT-G, the sequence of the screening steps is identical to scenario (1), except that it is assumed that no contact person will be lost to follow-up (i.e., by failing to return to the local Public Health office to have the result of the test read). We assume that a positive QFT-G result will reflect the same immunological reactivity as does the TST, i.e. that an infected person will have a positive test result 8–10 weeks following infection with MTB. This is stated in recent CDC recommendations for the use of QFT-G [23], but to our knowledge there are no systematic studies conducted that have directly compared the two tests up this point.

3) QFT-G for TST-positive contacts

All contact individuals are given a TST, followed by a QFT-G only for those who are TST-positive. It is presupposed that blood is collected into QFT-G tubes immediately after reading the TST; therefore, a third visit by the contact person is not necessary.

4) QFT-G only for those who are TST-positive and had been BCG-vaccinated.

Here, we assume that the BCG-vaccinated contacts have already been identified during the first survey before any test, which is the same for all contact individuals and, consequently, incurs no additional costs.

Discounting

Discounting reflects the higher value of money spent now as opposed to in the future. Owing to the short time span of the contact screenings, costs and outcomes (number of detective active TB cases) were not discounted.

Sensitivity analysis

In order to identify the threshold at which changes in probability estimates and cost values cause changes in the ranking of the screening strategies assessed in base-case analysis, univariate sensitivity analyses were conducted wherever appropriate. Therefore, except where otherwise stated, costs were halved and doubled to obtain lower and upper limits, respectively. Multivariate sensitivity analyses were performed on the costs for TST and QFT-G testing.

Costs

All costs are reported in 2004 Euro (except the 2005 costs for QFT-G and PPD RT 23 SSI Tuberculin) and presented in Table 2.

a) Personnel and material costs of the Public Health Service

At the central location for combating tuberculosis for Hamburg, where all X-ray examinations are performed, the Central Hamburg Public Health Department employed 3.5 medical technical assistants in 2004 with resulting total salary costs of € 197,280 [2.5 "BAT VIb" positions plus 1 "BAT Vb" position] including additional administrative costs of 15% and a lump office workplace fee. On the basis of an average of 211 work-days per year and a work-day of 7.7 hours (462

minutes), the resulting personnel expenses for one medical technical assistant were € 0.58 per minute.

The tasks of medical technical assistants employed there are limited to TB screening, i.e. X-ray examinations and the performance of all the tuberculin tests done for contact investigations. Besides the actual X-ray procedure, the X-ray examination also involves personnel organising an appointment for TST positive contacts to attend the examination. Upon failing to reply, these contact individuals again receive up to two further summons and, if necessary, are informed by telephone either personally or by their lodging providers (e.g. shelters for the homeless and other residences). Moreover, this work involves maintaining a registration site during office hours, explaining the examination procedure and filling in X-ray certificate card.

The personnel costs for the X-ray examination were calculated as follows: The necessary time expense was multiplied by the number of tuberculin tests performed in the year 2004, i.e. 2668 TST. An average time expense of 7 minutes was measured for the preparation and performance of the test. This results in personnel costs of € 4.06 per contact [*cAdmin*], i.e., € 10,832.0 for the 2668 TST.

The remaining personnel costs can be attributed solely to X-ray examinations and their associated organisational as well as documentary cost as described above (the sum of it here denoted as "X-ray procedure"), which amount to a total of € (197,280-10,832.08) or € 186,447.92. In 2004, 3276 X-ray examinations were conducted. This amounts to personnel expenses of € 56.91 per X-ray procedure. Additional to these are costs for the evaluation of the X-rays images by a specialist, which amounts to personnel costs of € 0.96 per minute. Such a physician needs 3 minutes to assess one image resulting in personnel expenses of € 2.89.

Further material costs are incurred for X-ray examination by using a digital X-ray apparatus. These costs comprise material and operating expenses, assuming a linear depreciation of the instrument over a period of 10 years. The acquisition costs of the applied X-ray system Phillips Diagnost CS 2 with a storage foil system "PCR AC 500" and observation station "Micora Store" amount to € 205,809.95 incl. VAT, i.e. € 20,581 per year with average, annual repair expenses, quality control tests and material costs of € 4,834.71 as well as maintenance costs of € 22,070.60. By dividing this by the number of examinations, each X-ray procedure thereby creates material expenses of € 14.50 (€ 47,486.31/3276). Consequently, the costs for the "performance of an X-ray examination" within the scope of a contact investigation (sum of the personnel costs for medical technical assistants and physician plus material costs) amount to a total of € 74.30 including administrative expenses [*cCXR*].

At the end of the screening tests (positive TST or QFT-G), a medical consultation is necessary for the contact person to choose between chemoprevention and another X-ray screening within the next 2 years. This also includes the detection of disease symptoms that become manifest between the X-ray appointments or thereafter and the precautionary measures to be taken as a result thereof. If the contact chooses to undergo chemoprevention this consultation will also include an explanation of the treatment, and the doctor will then refer the contact to a further pneumologist who has to be informed about the finding. This will take an average time of 25 minutes, which will incur doctor's expenses of € 24 (25 x € 0.96) [*cCons*]. A suspect X-ray finding, moreover, will require a further corresponding report, and an immediate organisation of more detailed diagnostics by a pneumologist/lung clinic. This will take an average of 40 minutes, thereby leading to costs of € 38.40 [*cSusp*].

The reading of the TST is performed by a doctor. By including documentation and a brief consultation (e.g. about additional measures to be taken upon strong reaction etc.), an average time

cost of 8 minutes was found, with corresponding personnel expenses of € 7.68 (8 x € 0.96) [*cRead*]. In the year 2004, 2540 TST of 2668 performed tests were read (*pRead* = 0.952).

b) Material costs of the TST

The TST licensed for Germany is PPD RT 23 2 T.U./0.1 ml of the Danish Statens Serum Institute (SSI), and distributed by Pharmore GmbH. The delivered price for 10 glass vials, each containing 1.5 ml of the RT 23/0.1 ml, is € 149.99 including 16.5% VAT. Because droplets always remain in the cannula and the vial, only 10 test doses of 2 T.U. are actually withdrawn from the 1.5ml vials [24]. According to the manufacturer's specifications, opened vials can be used only up to a maximum of 24 hours after withdrawal of the first dose. Whether only one or the maximum of 10 test doses per vial are used depends on the number of contact individuals tested per day. Consequently, the material costs per TST vary between € 1.5 and € 15. The mean dose amount of 5 test doses, with costs of € 7.5 per contact individual, is assumed as the base-case value in our analysis [*cRT23*].

d) Material and personnel costs of the QFT-G

The current charge made by a local private laboratory (Labor A. von Froreich, C. Schmidt & Partner) in Hamburg (as per March 1, 2005) is € 40 per contact individual, a price that includes the tubes for blood collection, IFN-γ ELISA materials, labour, and sample transport to the lab by a pick-up service [cLab]. The time for blood sampling is calculated to be equal to the time needed for performing the TST [cAdm]; nevertheless, this excludes the time for reading the TST. Material costs (syringes, cotton swabs, disinfection spray, bandages) are included – as for the application of the TST – in the fee for labour costs.

Compliance with INH-chemoprevention

Since INH-chemoprevention has not been routinely implemented in Germany, we assumed a base-case probability (*pPrev*) of only 50% that a contact individual diagnosed with LTBI will undergo an INH-chemoprevention.

Results

Base-case analysis

The model inputs for the test results, i.e., the probabilities of positive QFT-G, positive TST results and previous BCG vaccination, were obtained by direct extrapolation from the actual study data by normalising the ratios in Table 1 to a hypothetical cohort size of 1000 contact individuals to which each strategy was applied (see Table 2).

The costs for each strategy within a 2-year period were assessed by utilising the decision-tree model depicted in Figure 2 incorporating the data of Table 2. Applying the baseline criteria showed that the combined TST/QFT-G strategy is clearly less costly than the TST strategy alone (see Table 3). On the assumption of a 1% case-finding rate within the 2-year time frame, the cost of TST alone amounted to € 91.06 per close contact, greater than that of using QFT-G alone, which amounted to € 61.29 and would save € 29,770 per 1000 close contacts screened in comparison to TST alone. In a combination of both test procedures, whereby the QFT-G is only applied after a positive TST-result, the expenses were the least at € 52.05; a cost saving of € 39.01 per contact compared with the TST alone, but only € 9.24 compared with QFT-G alone. Further restricting the

QFT-G application (namely, to those contact individuals who are both TST-positive and previously BCG-vaccinated) was estimated to be slightly more expensive than the TST/QFT-G combination, due to a higher use of expensive X-ray examinations. Following our base case study data, applying QFT-G after a positive TST only 20.4% of subjects would have the subsequent, 3 chest X-ray examinations (see Table 2), whereas among TST-positive contacts in the TST/BCG/QFT-G strategy close to 30% (20% non-vaccinated TST positives plus 10.5% vaccinated TST positives which are QFT-G-positive) receive subsequent chest X-ray examinations. This X-ray cost outweighs the higher costs for QFT-G following the TST/QFT-strategy. Compared with the TST reference procedure, the costs here amount to € 55.45 – a saving of € 35.61 per close contact.

Sensitivity analysis

The bivariate threshold analysis of the impact of TST and QFT-G expenses on the cost relationship of the four test strategies is shown in Table 4. Even with continuous maximum use of a tuberculin PPD vial (i.e., with application of the TST for 10 contacts per day) incurring costs of only € 1.5 per RT 23-tuberculin dose, the QFT-G could cost up to € 67.8 and still remain the less expensive. Under base-case cost assumptions of € 7.5 per tuberculin dose the QFT-G alone remains cost-effective compared to TST at costs up to € 73.80. Conversely, the QFT-G-alone strategy is the most economical compared to TST-/QFT-G two step strategy only if the QFT-G price falls to € 27.20.

The TST/BCG/QFT-G screening option becomes the most economical only if there is a probability of ≥ 88% that the TST-positive contact individuals also have been BCG-vaccinated. When the incidence of TST-positive, previously BCG-vaccinated contacts is 66 %, however, the QFT-G-alone strategy would be less expensive (€ 61.30 versus € 61.60 per person) and switches to the second-cheapest position.

A doubling of the number of freshly detected contact individuals showing disease in the subsequent X-ray screening from 1% to 2% would hardly reduce the costs of the sole TST-screening (€ 91.06 versus € 90.94, and therefore would not change the relative ranking of the costs of the individual strategies. This relationship stays robust even with maximum variation of compliance with INH-chemoprevention of 0 to 100%.

On the other hand, the TST strategy becomes a more efficient alternative to the QFT-G procedure when the percentage of TST-positive individuals in the examined cohort of contact persons falls below 26%. However, a doubling of the percentage of QFT-G-positive individuals in our cohort to 20%, with resulting screening costs of € 78.50 per person, does not change the ranking.

If the Public Health Service were to cease performing X-ray examinations and outsource this activity to the private sector, a cost of € 29.38 (€ 16.32 multiplied by the customarily applied factor 1.8 for no.5130 of the *Gebührenordnung für Ärzte*, the German national reimbursement catalogue) would be paid per contact examination. Taking this cost as lower limit in sensitivity analysis, the X-ray cost could be substantially reduced to € 53.52 per examination, but TST-based screening would still be the most expensive (see Table 3). It must also be borne in mind that the radiologist in private practice would not perform any service apart from the X-ray examination. The organizational and counseling work involved in following up TST- and/or QFT-G-positives would still be the responsibility of the Public Health Service, and at significant cost.

Discussion

The present analysis demonstrates that the combination of traditional TST and a new IFN-γ test in the investigation of close contacts is, from the perspective of the Public Health Service,

considerably less expensive under the base-case assumptions employed than one procedure alone. Because of the small number of successive chest X-ray examinations, the application of the QFT-G for TST-positive patients is far more efficient than the TST alone, which seems comparably inexpensive at first.

More than one-half of the contacts (157/309, 50.3%) had previously been BCG vaccinated, and this was independent of their origin (German or foreign-born) and their age, because in Germany BCG vaccination was recommended up to March 1998. Recently published studies suggest most positive TST results in BCG vaccinated individuals are false positive [21, 22, 25]. However, a further differentiation in respect of BCG anamnesis does not bring additional advantages in comparison with the combination of TST and QFT-G, since even with a high percentage of previously BCG-vaccinated contacts, the smaller fraction of TST-positive but BCG-unvaccinated individuals – in our analysis, about 20% of the TST-positive patients – still have to undergo the costly, triple X-ray screening procedure.

Use of INH prophylaxis for only those people who are both TST and QFT-G positive (and considering only these as having true MTB infection) would avoid prescribing of unnecessary preventive treatment (with associated costs and possible side-effects) to contacts with false positive TST responses. Using such a strategy, the cost-effectiveness of INH-chemoprevention may further increase over that recently reported [9].

Our study has some limitations. It considers the best available cost data for a Public Health Service contact investigation programme already being implemented in a major German city. We attempted to take into account possible differences between costs for public health and local laboratory services incurred in Hamburg and at other locations by conducting sensitivity analyses. However, these cannot take into consideration future reductions in the cost of X-ray equipment, changes in wage structures for Public Health Service employees, or when and how cost-saving structural changes consequent upon a new screening strategy could be implemented. Indeed, although the

proper question to ask from an economist's viewpoint is not that of whether a less expensive strategy will work in practise, but rather that of when it should be implemented, concerns about organisational convenience may also influence any decision to change the process of contact investigation. Therefore, it remains to be seen whether in the future the absolutely most cost-efficient strategy or a slightly more expensive but simpler procedure – in this case, the exclusive use of the QFT-G – will prevail in the diagnosis of LTBI.

The results of our cost-minimisation analysis depend more on contributory costs than on associated probabilities. However, these results do depend decisively on the prevalence of MTB-infected individuals: Since the TST strategy becomes the less expensive alternative when the percentage of TST-positive individuals falls below 26% (with considerably fewer successive chest X-ray examinations), a careful differentiation between close and distant contacts may be important. A higher rate TST-positivity would be expected with the investigation of close contacts. However, using the TST as the first screening option and not QFT-G could possibly exclude a considerable number of people with false negative TST responses but likely to be QFT-G positive [14]. This may be especially the case in immunosuppressed contacts, such as those HIV-positive, and thus in a community with many HIV positive patients the TST/QFT-G two-step strategy should be reassessed if there are such particular epidemiologic conditions.

In conclusion, screening for TB by introducing a new whole-blood IFN-γ test as a replacement for the TST, or especially by combining TST and QFT-G in the investigation of close contacts, may markedly reduce Public Health costs compared with the current procedure of using the TST only.

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Table 1. Results of TST and QFT-G testing in a population of 309 close contacts, stratified by BCG vaccination.

QFT-G result			Previous BCG vaccination		
			no	yes	total
negative	TST	negative	122	47	169
		positive	13	96	109
		total	135	143	278
positive	TST	negative	3		3
		positive	14	14	28
		total	17	14	31

Table 2: Base-case estimates and ranges used in cost-minimisation analysis

Variables	Base-case	Range	Reference
External costs [€]			
Per tuberculin dose [cTub]	7.5	1.5-15	Pharmore price list
Per QFT-G-test result (labour and QFT tubes) [cLab]	40	20-80	Laboratory provider
Outcome of contact investigation			
Proportion of contacts suspected of having TB disease (%)	1	0-2	15,16,17,18
Public Health Service costs [€]			
Reading and registering TST result (doctor;8 minutes) [cRead]	4.06	-	Observed
Consulting contacts without TB disease (doctor;25 minutes) [cCons]	24	-	Observed
Administering the TST (MTA; 7 minutes) [cAdm]	7.68	-	Observed
Sampling blood for QFT-G (MTA; 7 minutes) [cAdm]	7.68	-	Observed
Cost for read TST per contact [cTST (cRT23 + cAdm + cRead)]	19.24	13.24-26.74[1]	Calculated
Cost for unread TST per contact [cTSTm (cRT23 +cAdm)]	15.18		Calculated
Cost for QFT testing [cQFT (cLab +cAdm)]	47.68	27.68-87.68[2]	

Per chest X-ray examination [cCXR]	74.3	(29.38[3])	Calculated
Total cost for QFT-based screening per contact [tcQFT (cQFT + cCXR + cCons)]	See note 4		Calculated
Total cost for TST-based screening per contact [tcTST (cTST + cCXR + cCons)]	See note 4		Calculated
Managing diagnostics for suspected contacts (doctor; 40 minutes) [cSusp]	See note 4		Calculated
Total cost for TST-based screening per contact suspected of having TB disease [tcTSTs (cTST+cCXR +cSusp)]	See note 4		Calculated
Total cost for QFT-G-based screening per contact suspected of having TB disease [tcQFTs (cQFT+cCXR +cSusp)]	See note 4		Calculated

continued

Variables	**Base-case**	**Range**	**Reference**
Test result probabilities			
Proportion of TST-positive contacts [pTST]	0.44	-	Study data (see Table 1)
Proportion of QFT-G-positive contacts [pQFT]	0.1	-	Study data (see Table 1)
Proportion of QFT-G-positive contacts among TST-positive contacts [pQFTt]	0.204	-	Study data (see Table 1)
Proportion of BCG vaccinated contacts among TST-positive contacts [ppBCG]	0.804	-	Study data (see Table 1)
Proportion of QFT-G-positive contacts among BCG-vaccinated contacts [pQFTb]	0.13	-	Study data (see Table 1)
Probability of reading TST result [pRead]	0.952	-	Observed
Probability of opting for INH-chemoprevention [pPrev]	0.5	0-1.0	Assumption
Probability of evidence of active TB per X-ray examination [pTB]	0.0033	0-0.0066	Weighted[5] from base-case estimate

[1] Varies with cost per tuberculin dose.
[2] Varies with cost per QFT-G tube and labour.

[3] Cost of referral of the contact person to a radiological practice used as lower limit (factor 1.8, see text).
[4] Total cost depends on the incidence of chest X-ray examinations. Contacts without radiological evidence of active TB will receive three examinations; suspected contacts drop out of the follow-up by the public health service.
[5] The probability of a suspect result in the series of three chest X-ray examinations is 1%; this is assumed to be equally distributed between the individual examinations.

Table 3. Economic outcomes

Variables	Base-case	Lower Limit	Upper Limit
a) Varying cost of RT 23			
Total saving (cost) relative to TST screening, per 1000 close contacts, €			
TST/QFT-G	39,010	39,010	39,010
TST/BCG/QFT-G	35,610	35,610	35,610
QFT	29,770	22,280	37,270
Cost per contact investigated, €			
TST only	91.06	85.06	98.56
QFT	61.29	61.29	61.29
TST/QFT-G	52.05	46.05	59.55
TST/BCG/QFT-G	55.45	49.45	62.95
b) Varying cost of QFT-G			
Total saving (cost) relative to TST screening, per 1000 close contacts, €			
TST/QFT-G	39,010	42,340	22,250
TST/BCG/QFT-G	35,610	47,380	22,100
QFT	29,770	49,770	(*–10,230*[a])
Cost per contact investigated, €			
TST only	91.06	91.06	91.06
QFT	61.29	41.29	101.29
TST/QFT-G	52.05	43.68	68.81
TST/BCG/QFT-G	55.45	48.72	68.90
c) Varying probability of opting for INH-chemoprevention			
Total saving (cost) relative to TST screening, per 1000 close contacts, €			
TST/QFT-G	39,010	63,670	14,340
TST/BCG/QFT-G	35,610	57,250	13,960
QFT	29,770	53,350	6,160
Cost per contact investigated, €			
TST only	91.06	122.04	60.07
QFT	61.29	68.69	53.89
TST/QFT-G	52.05	58.37	45.73
TST/BCG/QFT-G	55.45	64.79	46.11

continued

Variables	Base-case	Lower Limit	Upper Limit
d) Varying probability of suspect X-ray results			
Total saving (cost) relative to TST screening, per 1000 close contacts, €			
TST/QFT-G	39,010	39,090	39,910
TST/BCG/QFT-G	35,610	35,690	35,530
QFT	29,770	29,850	29,670
Cost per contact investigated, €			
TST only	91.06	91.17	90.94
QFT	61.29	61.32	61.27
TST/QFT-G	52.05	52.08	52.03
TST/BCG/QFT-G	55.45	55.48	55.41
e) Varying cost of chest X-ray[b]			
Total saving (cost) relative to TST screening, per 1000 close contacts, €			
TST/QFT-G	39,010	1,190	-
TST/BCG/QFT-G	35,610	9,130	-
QFT	29,770	9,390	-
Cost per contact investigated, €			
TST only	91.06	53.52	-
QFT	61.29	52.33	-
TST/QFT-G	52.05	44.39	-
TST/BCG/QFT-G	55.45	44.13	-

[a]Additional expenditure instead of saving.
[b]No upper limit assumed in comparison with base-case cost.

Table 4. Threshold analysis referring to base-case ranking

Variables	Value	Change in ranking
Decrease in proportion of TST-positives	≤ 26%	TST-based strategy less expensive than QFT-G-based strategy
Reduction in cost of QFT-G,		
a) base-case assumption	≤ 27.20 €	QFT-G-based strategy least expensive
b) lowest cost of RT 23 (€ 1.5 per dose)	≤ 17.5 €	QFT-G-based strategy least expensive
Increase in proportion of BCG vaccinees	≥ 88%	TST/BCG/QFT-G-based strategy least expensive
Decrease in proportion of BCG vaccinees	≤ 66%	QFT-G-based strategy less expensive than TST/BCG/QFT-G-based strategy
Increase in cost of QFT-G,		
a) base-case assumption	≥ 73.8 €	TST-based strategy less expensive than QFT-G-based strategy
b) lowest cost of RT 23 (€ 1.5 per dose)	≥ 67.8 €	TST-based strategy less expensive than QFT-G-based strategy

Figure 1. Flowchart for the examination of close contacts of infectious TB cases in Germany.

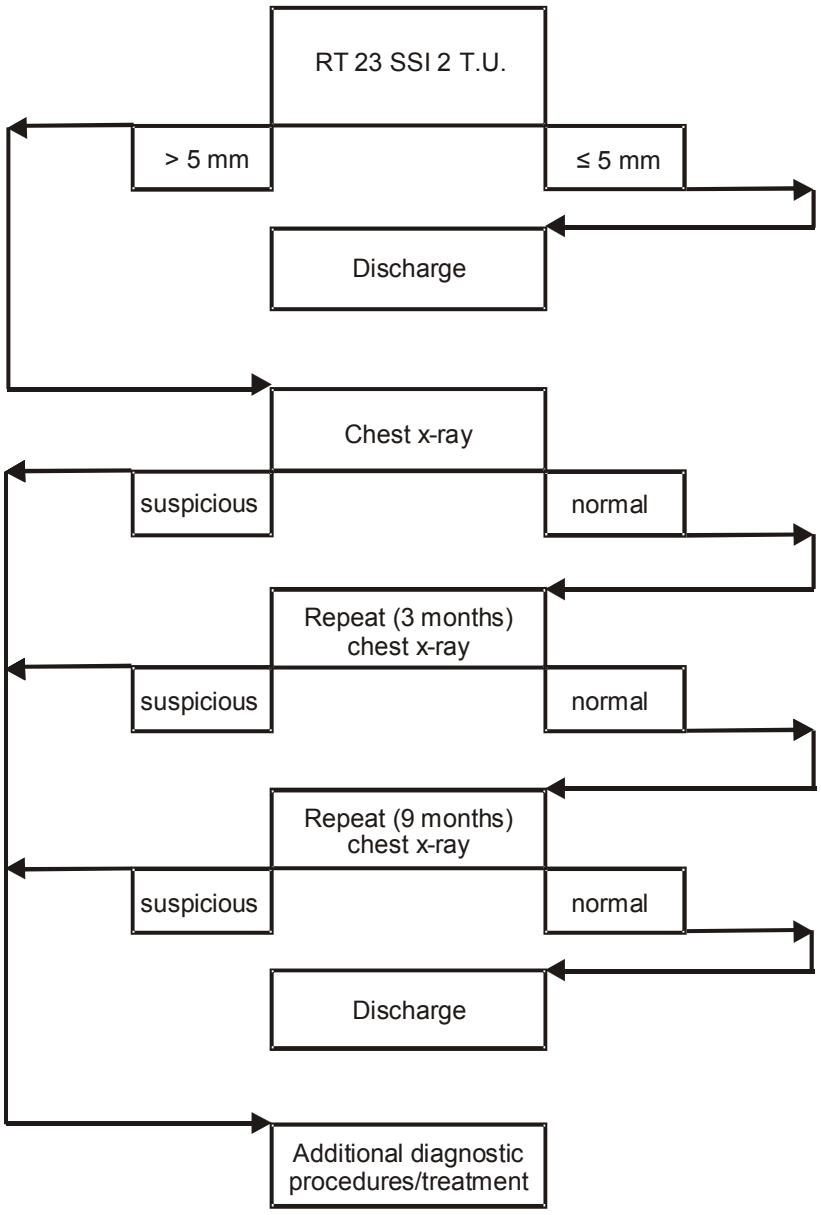
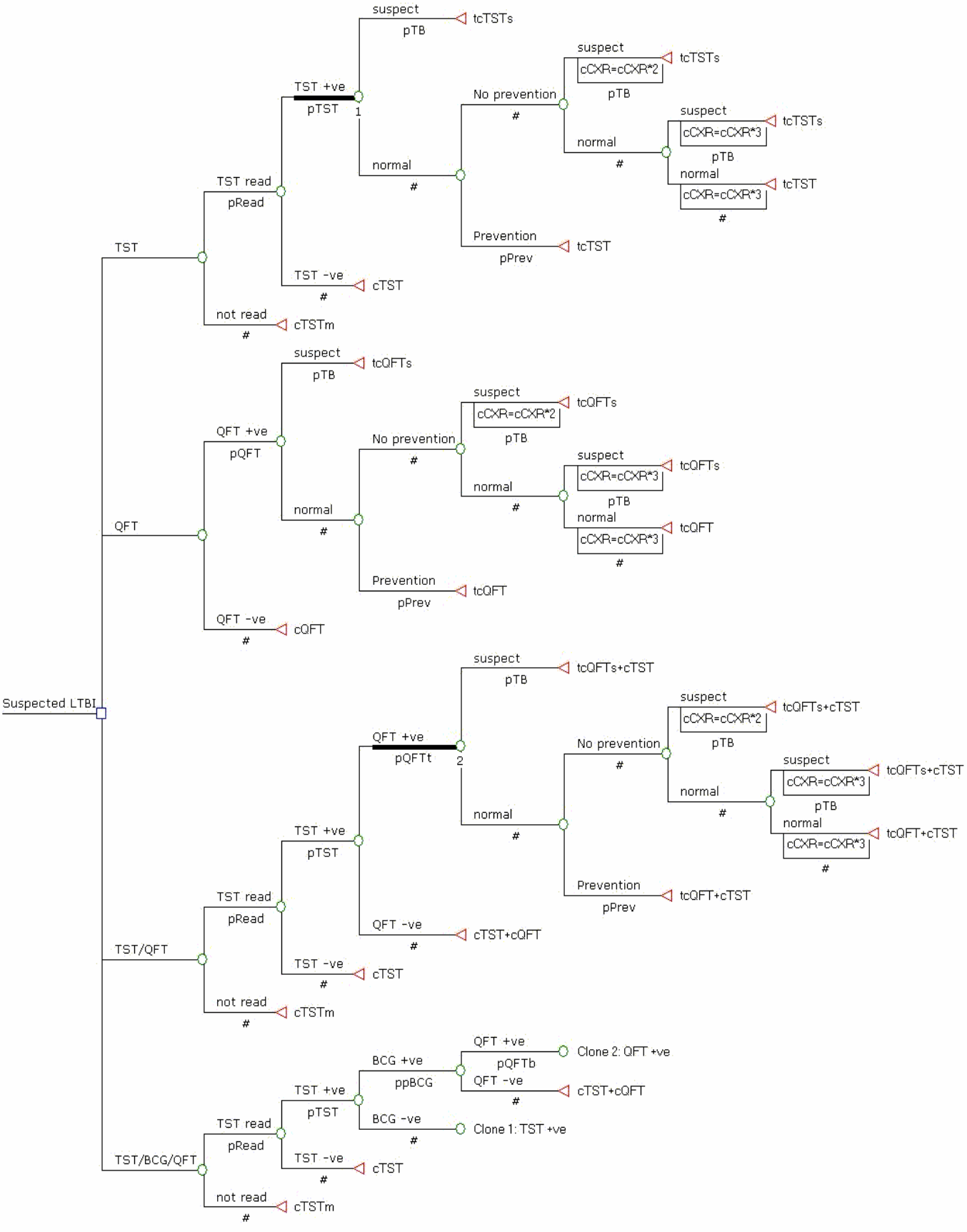


Figure 2. Decision trees for four different strategies of contact investigation


Suspected LTBI
TST
TST read
pRead
TST +ve
pTST
1
suspect
pTB
tcTSTs
normal
#
No prevention
#
suspect
cCXR=cCXR*2
pTB
tcTSTs
normal
#
suspect
cCXR=cCXR*3
pTB
tcTSTs
normal
cCXR=cCXR*3
#
tcTST
Prevention
pPrev
tcTST
TST -ve
#
cTST
not read
#
cTSTm
QFT
QFT +ve
pQFT
suspect
pTB
tcQFTs
normal
#
No prevention
#
suspect
cCXR=cCXR*2
pTB
tcQFTs
normal
#
suspect
cCXR=cCXR*3
pTB
tcQFTs
normal
cCXR=cCXR*3
#
tcQFT
Prevention
pPrev
tcQFT
QFT -ve
#
cQFT
TST/QFT
TST read
pRead
TST +ve
pTST
QFT +ve
pQFTt
2
suspect
pTB
tcQFTs+cTST
normal
#
No prevention
#
suspect
cCXR=cCXR*2
pTB
tcQFTs+cTST
normal
#
suspect
cCXR=cCXR*3
pTB
tcQFTs+cTST
normal
cCXR=cCXR*3
#
tcQFT+cTST
Prevention
pPrev
tcQFT+cTST
QFT -ve
#
cTST+cQFT
TST -ve
#
cTST
not read
#
cTSTm
TST/BCG/QFT
TST read
pRead
TST +ve
pTST
BCG +ve
ppBCG
QFT +ve
pQFTb
Clone 2: QFT +ve
QFT -ve
#
cTST+cQFT
BCG -ve
#
Clone 1: TST +ve
TST -ve
#
cTST
not read
#
cTSTm

Legend: Decision analysis model for predicting the costs of four alternative screening strategies in a cohort of adult close contacts. A decision node (□) is the decision to test a contact by using the TST or QFT-G. Branches from a change node (o) represent the possible outcomes of an event; terminal nodes (◁) are assigned the cost of a prior series of actions and events. Probabilities (p): pRead: probability of TST being read; pTB: probability of an infected contact developing active disease; ppBCG: probability of a TST-positive contact having received BCG vaccination; pQFT: probability of QFT-G being positive; pQFTb: probability of QFT-G being positive in BCG-vaccinees; pQFTt: probability of QFT-G being positive in TST-positive contacts; pTST: probability of TST result being positive; pPrev: probability of a contact receiving INH chemoprevention. #: complementary probability (all probabilities of chance node´s branches to sum to 1.0).

Cost (c) and total cost (tc): Definitions see Table 2.