

Economic evaluation of the use of PCR assay in diagnosing pulmonary TB in a low-incidence area

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ABSTRACT: To determine whether polymerase chain reaction (PCR) testing in the initial diagnosis of pulmonary tuberculosis (TB) is cost-effective in a low-prevalence population, an economic evaluation was carried out between the smear and culture (NOPCR) and smear, culture and PCR (+PCR) strategies.

A decision tree model based on retrospective laboratory data was developed to assess the strategies of testing patients with suspicion of TB. Direct healthcare costs prior to confirmation of TB or nontuberculous mycobacteria by PCR or culture were included. Effectiveness was measured by the probability of correct treatment and isolation decisions.

In the baseline situation NOPCR costs €29.50 less than the +PCR strategy per patient tested. According to sensitivity analyses, reducing PCR test price, shortening test performance time or increasing the proportion of smear-positive patients in the tested population would contribute to cost savings with the +PCR strategy.

Routine polymerase chain reaction testing of all specimens from suspected tuberculosis patients in a low-prevalence population was not cost-saving. When the polymerase chain reaction assay was applied only to smear-positive sputum specimens, the smear and culture strategy was clearly dominated by it, i.e. the polymerase chain reaction smear-positive sputum strategy was less costly and more effective in producing correct treatment decisions and isolations.

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To date the global tuberculosis (TB) epidemic has shown no notable decline. In low-prevalence countries, factors contributing to the spread of the disease, especially in hospital settings, are delays in diagnosis and initiation of treatment [1]. In addition to lack of suspicion of TB, diagnosis is prolonged by the time-consuming identification of the *Mycobacterium tuberculosis* complex in sputum specimens [2]. The acid-fast smear rapidly identifies patients with infectious TB, but is neither sensitive nor specific for *M. tuberculosis* bacteria. In countries like Finland (494 TB cases and 505 cases with nontuberculous mycobacteria in 2001) where nontuberculous mycobacteria are frequently detected, smear-positive nontuberculous cases may be isolated and treated with inappropriate drug combinations unnecessarily until culture results are available. Culture is sensitive in detecting mycobacteria for species identification and susceptibility testing, but requires a mean time of 2–3 weeks [3]. In smear-negative TB cases this may lead to unnecessary diagnostic procedures that increase healthcare costs and cause distress to the patients.

Commercial nucleic acid amplification (NAA) assays are rapid, sensitive and specific tools for the detection of the *M. tuberculosis* complex in sputum specimens [4–6]. In addition to rapid differentiation between this complex and nontuberculous mycobacteria in smear-positive sputum specimens, NAA assays detect a considerable proportion of

smear-negative culture-positive TB cases [4, 6, 7]. However, the implementation and performance of these tests demands financial resources and experienced laboratory personnel; therefore the cost-effectiveness of NAA assays in diagnosing pulmonary TB should be carefully assessed.

Finland is classified as a low-prevalence country with the TB incidence below 10 per 100,000 inhabitants since 2001. In order to make an economic evaluation of two different strategies (smear, culture and polymerase chain reaction (PCR) testing to all specimens (+PCR), and smear and culture testing to all specimens, no PCR testing (NOPCR)) in diagnosing pulmonary TB in a low-prevalence population, a decision tree model was developed. For cost-minimisation analysis, all direct healthcare costs were included, prior confirmation or exclusion of TB or nontuberculous mycobacteria by culture or PCR. Effectiveness was measured by the probability of correct treatment and isolation decisions.

Materials and methods

A decision tree was developed to compare the expected costs and outcomes of two strategies for diagnosing pulmonary TB: the conventional NOPCR strategy currently used, based on smear and culture tests, and the +PCR strategy, in

which a PCR test is performed on sputum specimens in addition to smear and culture. The model shows the paths from initial suspicion of TB to eventual outcomes with their associated probabilities and costs (fig. 1). In this analysis, the tree was used to calculate the expected cost per patient and the probability of correct treatment and isolation decisions for each strategy. The decision-making in the model proceeds according to the available test results and the patient's clinical picture. The baseline probabilities used in the decision tree were based on retrospective patient data from the 2-yr period 1997–1998. To level off yearly fluctuations in low-prevalence areas, the combined annual data of two large Finnish University Hospital Districts (Pirkanmaa and Varsinais-Suomi, populations of 446,000 and 449,000 inhabitants, respectively) were applied. The description of the branches and calculations of the baseline probabilities are presented in table 1.

The baseline performance values for the PCR test were obtained from the study performed earlier in the Pirkanmaa Hospital District [6]. In that study 367 sputum specimens from 169 patients were tested by auramine fluorescent and Ziehl-Neelsen stain, Löwenstein-Jensen and radiometric liquid culture system cultures (BACTEC; Becton Dickinson Diagnostic Instrument Systems, MD, USA) and by the Cobas Amplicor PCR method (Roche Diagnostics, Basel, Switzerland).

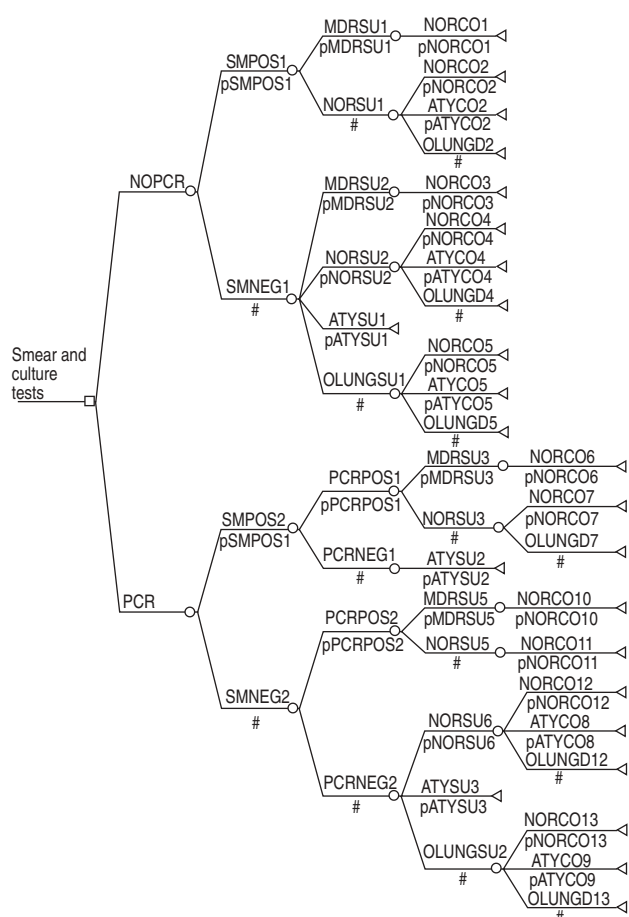


Table 1. – Abbreviations, descriptions and baseline probabilities used in decision tree analysis

Branch	Description	n	Probability		
			Variable	Description	Value
SMPOS1	Smear positive	38	pSMPOS1	SMPOS1 [#] /N [‡]	0.031
MDRSU1	Multidrug-resistant TB suspected	3	pMDRSU1	MDRSU1 [§] /SMPOS1	0.079
MDRSU2	Multidrug-resistant TB suspected	1	pMDRSU2	MDRSU2 [§] /SMNEG1 ⁺	0.001
MDRSU3	Multidrug-resistant TB suspected	3	pMDRSU3	MDRSU3 [§] /PCRPOS1	0.150
MDRSU5	Multidrug-resistant TB suspected	1	pMDRSU5	MDRSU5 [§] /PCRPOS2	0.167
NORSU2	Drug-sensitive TB suspected	10	pNORSU2	NORSU2 [§] /SMNEG1	0.008
NORSU6	Drug-sensitive TB suspected	3	pNORSU6	NORSU6 [§] /PCRNEG2	0.003
ATYSU1	Nontuberculous mycobacteria suspected	21	pATYSU1	ATYSU1 [§] /SMNEG1	0.018
ATYSU2	Nontuberculous mycobacteria suspected	18	pATYSU2	ATYSU2 [§] /PCRNEG1	1.000
ATYSU3	Nontuberculous mycobacteria suspected	21	pATYSU3	ATYSU3 [§] /PCRNEG2	0.018
PCRPOS1	PCR positive	20	pPCRPOS1	PCRPOS1/SMPOS2 [#]	0.526
PCRPOS2	PCR positive	6	pPCRPOS2	PCRPOS2/SMNEG2 ⁺	0.005
NORCO1	Drug-sensitive TB confirmed	3	pNORCO1	NORCO1/MDRSU1	1.000
NORCO2	Drug-sensitive TB confirmed	16	pNORCO2	NORCO2/NORSU1	0.457
NORCO3	Drug-sensitive TB confirmed	1	pNORCO3	NORCO3/MDRSU2	1.000
NORCO4	Drug-sensitive TB confirmed	5	pNORCO4	NORCO4/NORSU2	0.500
NORCO5	Drug-sensitive TB confirmed	1	pNORCO5	NORCO5/OLUNGSU1	0.001
NORCO6	Drug-sensitive TB confirmed	3	pNORCO6	NORCO6/MDRSU3	1.000
NORCO7	Drug-sensitive TB confirmed	16	pNORCO7	NORCO7/NORSU3	0.941
NORCO10	Drug-sensitive TB confirmed	1	pNORCO10	NORCO10/MDRSU5	1.000
NORCO11	Drug-sensitive TB confirmed	5	pNORCO11	NORCO11/NORSU5	1.000
NORCO12	Drug-sensitive TB confirmed	1	pNORCO12	NORCO12/NORSU6	0.333
NORCO13	Drug-sensitive TB confirmed	1	pNORCO13	NORCO13/OLUNGSU2	0.001
ATYCO2	Nontuberculous mycobacteria confirmed	15	pATYCO2	ATYCO2/NORSU1	0.429
ATYCO4	Nontuberculous mycobacteria confirmed	4	pATYCO4	ATYCO4/NORSU2	0.400
ATYCO5	Nontuberculous mycobacteria confirmed	2	pATYCO5	ATYCO5/OLUNGSU1	0.002
ATYCO8	Nontuberculous mycobacteria confirmed	1	pATYCO8	ATYCO8/NORSU6	0.333
ATYCO9	Nontuberculous mycobacteria confirmed	5	pATYCO9	ATYCO9/OLUNGSU2	0.004

[#]: n=38, including 19 patients with tuberculosis (TB), 15 with nontuberculous mycobacteria and four with negative cultures; [‡]: baseline population, n=1,219; ⁺: n=1,181, including eight patients with TB and 20 patients with nontuberculous mycobacteria; [§]: based on expert opinion.

Table 2. – Unit costs used in decision tree analysis

Cost items	€
TB isolation 14 days	4768.10
TB medication per week	26.70
Laboratory tests, isolation	20.70
Multidrug-resistant TB isolation 14 days	4768.10
Multidrug-resistant TB medication per month	165.80
Inpatient care per day	169.00
Outpatient visit	64.70
Smear and culture ×3	70.60
PCR test ×3	126.10
Chest radiograph	27.20
Laboratory tests, control	17.70
High resolution computed tomography	154.10
Bronchoscopy	235.10
Medication against infection	27.80

TB: tuberculosis; PCR: polymerase chain reaction.

the price of the PCR test and the probability of smear-positive patients, with which the +PCR strategy may be cost-saving (fig. 2).

Results

The baseline population in the decision tree model was 1,219 patients, including 27 (2.2%) culture-proven pulmonary TB patients and 35 (2.8%) patients with nontuberculous mycobacteria. No MDR TB patients were detected in the study districts during 1997–1998, while two MDR cases were

reported overall in Finland during that period. The proportion of smear-positive patients was 3.1%. Of the 38 smear-positive patients, 19 were TB patients and 15 patients had nontuberculous mycobacteria. Furthermore, four patients proved positive by smear but negative by culture, most probably due to slowly growing or unculturable nontuberculous mycobacterial species.

The results of the base case situation and sensitivity analyses are presented in tables 3 and 4. In the base case, where PCR results were available in 4 days and culture results in 2 weeks, the cost per patient tested in the NOPCR strategy was €29.50 (12%) less than in the +PCR strategy (table 3). Prolonging culturing time to 3 weeks did not change this result. In the ideal setting for PCR, in which PCR is performed daily and the culturing time is 3 weeks, the +PCR strategy would save €8.90 per patient tested compared with the NOPCR strategy (table 3).

The model proved to be sensitive to the proportion of smear-positive patients in the base case population and to the cost of the PCR test. With baseline assumptions the threshold analysis showed that if the proportion of smear-positive patients in the tested population were over 4.0%, the PCR strategy would be cost-saving. Similarly, if the cost of the PCR test (including a set of three sputum tests) was ≤€97, the +PCR strategy would reduce costs compared with NOPCR. Additionally, threshold analysis revealed that if isolation expenses rose above €5,965 per case isolated in the base situation, the +PCR strategy would be less costly. The model was robust to changes both in the probability of smear-positive PCR-positive cases (pPCRPOS1) and smear-negative PCR-positive cases (pPCRPOS2) and no threshold values in reasonable ranges were found (table 4). Furthermore, two-way sensitivity analysis indicates that the less expensive PCR

Table 3. – The results of base case and sensitivity analyses

Analysis	Strategy	Cost/patient tested €	Incremental cost €
Base analysis	NOPCR	225.40	
PCR results in 4 days, culture results in 2 weeks	+PCR	254.90	29.50
Sensitivity analysis 1	NOPCR	226.40	
PCR results in 4 days, culture results in 3 weeks	+PCR	254.90	28.50
Sensitivity analysis 2	NOPCR	226.40	
PCR results in 1 day, culture results in 3 weeks	+PCR	217.50	-8.90
Sensitivity analysis 3	NOPCR	225.40	
PCR results in 4 days, culture results in 2 weeks	+PCR SMPOS	130.00	-95.40

NOPCR: smear and culture testing to all specimens, no polymerase chain reaction (PCR) testing; +PCR: smear, culture and PCR testing to all specimens; +PCR SMPOS: smear and culture testing to all specimens, and PCR testing only to smear-positive specimens.

Table 4. – The variables selected for threshold analysis and its results (base case)

Variable	Range	TV	Optimal strategy, if variable value <TV	Optimal strategy, if variable value >TV
Probabilities				
pSMPOS1	0.01–0.08	0.04	NOPCR	+PCR
pPCRPOS1	0.35–0.70	No threshold		
pPCRPOS2	0.001–0.09	No threshold		
Costs €				
PCR [#]	50–200	96.60	+PCR	NOPCR
TBISO	4500–6000	5964.60	NOPCR	+PCR
MDRISO	4500–6000	No threshold		

TV: threshold value; pSMPOS1: probability of smear-positive patients; pPCRPOS1: probability of smear and polymerase chain reaction (PCR)-positive patients; pPCRPOS2: probability of smear-negative, PCR-positive patients; TBISO: isolation of drug-sensitive tuberculosis (TB) patient for 14 days; MDRISO: isolation of multidrug-resistant TB patient for 14 days. [#]: set of three PCR tests per patient.

testing is, the smaller the proportion of smear-positive patients in the tested population can be for the +PCR strategy to be cost-saving (fig. 2). The threshold value for the cost of a PCR test (a set of three tests) can be determined from figure 2 when the incidence of smear-positive patients in the population is known.

The effectiveness of the +PCR and NOPCR strategies in terms of correct treatment and isolation decisions was also evaluated. In the base case situation the incremental cost turned out to be €1,970 for one additional correct treatment decision and €2,011 for an additional correct isolation with the +PCR strategy.

The alternative strategy of applying PCR testing only to smear-positive sputum specimens (+PCR SMPOS strategy) proved to be cost-effective and dominated the NOPCR strategy, which means that in addition to being clearly less costly (€95.30 per patient cheaper), more correct treatment decisions were obtained (1.47 percentage points difference in favour of +PCR SMPOS strategy) and almost one-half of isolations were avoided with the +PCR SMPOS strategy (table 5).

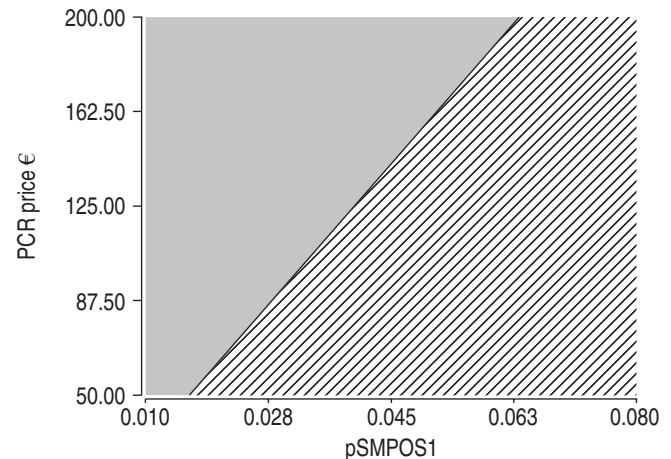


Fig. 2. – Two-way sensitivity analysis with polymerase chain reaction (PCR) price and proportion of smear-positive patients in the population (pSMPOS1). ■: NOACR strategy is cost-saving; ▨: +PCR strategy is cost-saving.

Table 5. – Cost-effectiveness analysis of correct treatment and isolation decisions

Strategy	Cost per patient tested €	Incremental cost €	Effectiveness [#]	Incremental effectiveness	Cost-effectiveness ratio €	Incremental cost-effectiveness ratio
Correct treatment decisions						
+PCR SMPOS	130.00		0.9716		133.84	
NOPCR	225.40	95.30	0.9569	-0.0147	235.52	Dominated
Correct isolation decisions						
+PCR SMPOS	130.00		0.0302		4308.55	
NOPCR	225.40	95.30	0.0155	-0.0147	14543.73	Dominated

+PCR SMPOS: smear and culture testing to all specimens, and PCR testing only to smear-positive specimens; NOPCR: smear and culture testing to all specimens, no PCR testing. [#]: probability of correct decision.

Discussion

Rapid confirmation of TB diagnosis is an essential part of the TB control strategy. Features such as standardised reagents, automated reading of reaction results, detection of inhibition and rapidity of the test make Amplicor PCR suitable for a routine screening test for *M. tuberculosis* detection [10]. It cannot, however, replace the smear, which determines infectiousness, or culture, which is essential in species identification and susceptibility testing. Furthermore, combined use of these three tests is limited mainly by the cost of PCR testing, and therefore, economic evaluation is needed to assess the role of PCR testing.

According to the present data the NOPCR strategy was cost-saving compared with +PCR when the PCR assay was applied to all specimens from suspected TB patients and performed twice a week. The sensitivity analyses indicated three significant factors contributing to the costs of the +PCR strategy: the performance time and the cost of the PCR assay, as well as the proportion of smear-positive patients in the base population.

Performing the PCR assay twice a week is a realistic frequency in a low-prevalence area. More frequent test runs would demand larger numbers of specimens, whereas testing once a week would compromise the rapidity of the PCR assay, which is its most important feature. The current PCR test expenses originate predominately from expensive reagents. Reducing the number of sputum specimens tested per patient from three to two would reasonably decrease the costs. However, multiple specimens are required to maximise the sensitivity of the PCR test in the detection of *M. tuberculosis* especially in smear-negative specimens, and to confirm the exclusion of *M. tuberculosis* in smear-positive specimens [6, 7, 10]. The fact that patients expectorate bacteria infrequently and specimens are of inconsistent quality is supported by the findings of NELSON *et al.* [11] in which 13% of smear-positive and 7% of smear-negative TB cases were detected by conventional tests only from the third sputum specimen tested.

According to two-way sensitivity analysis, the expenses of the PCR strategy could be reduced by controlling the proportion of smear-positive patients in the population tested. In this model, only 3.1% of patients were positive by smear and 2.1% had pulmonary TB confirmed by culture, reflecting an unnecessarily low threshold among clinicians in suspecting pulmonary TB. It may be explained by scanty clinical experience of TB in public healthcare facilities, whereas in hospital settings sputum examination for *M. tuberculosis* may be performed routinely for most patients with respiratory symptoms. In a study by DIVINAGRACIA *et al.* [12], sputum testing by smear and culture was indicated in only ~53% of all suspected TB cases; nevertheless no TB cases were missed. Further, a clinical risk assessment for TB suspicion proved to help targeting patient populations who would benefit from PCR testing [13]. More accurate selection of patient population would reduce unnecessary testing of patients with other diseases. However, in a low-prevalence population the total number of submitted specimens would decrease to a level where performing PCR tests would be appropriate only once a week. This may be avoided by centralising specimen testing in one laboratory centre, but consequent transportation, specimen handling and result service are matters still to be resolved and were not evaluated in this study.

The results of the analysis were robust to changes in the probability of smear-positive PCR-positive cases (pPCRPOS1), which reflects the sensitivity of the PCR test for smear-positive TB cases (table 4). This is explained by those smear-positive TB patients misdiagnosed as patients with

nontuberculous mycobacteria who would incur no additional costs in the model prior to culture confirmation. However, epidemiologically these infectious smear-positive TB patients would have a notable impact on TB control. The threshold value for pPCRPOS2, expressing the sensitivity of the PCR test for smear-negative TB cases, was not detected due to the small proportion of smear-negative TB patients in the population tested. A clinician's likelihood to suspect the correct diagnosis with an accuracy of 70% in smear-negative patients may have been overestimated in the model. However, sensitivity analysis revealed that the economic benefit of the NOPCR strategy remained unchanged even when the accuracy of suspicion was only 50%. This is also explained by the small proportion (0.7%) of smear-negative TB patients in the population, and hence its minimal effect on the total costs of the laboratory strategies.

In the baseline situation PCR testing of all suspected TB patients was not profitable in a low prevalence country. It cost €29.50 more per patient tested and the cost for one additional correct treatment decision was €1,970. General assessment of acceptable incremental cost for applying PCR strategy was not feasible in this study. It is highly dependent on the local TB infection control strategy and fiscal framework, and has to be evaluated separately in each setting concerned.

The highest expenses per patient in both strategies originated from isolation and treatment of smear-positive patients. The average cost per smear-positive patient was €5,006 in the NOPCR strategy and €1,931 in +PCR. Isolation room costs may constitute up to 87% of total costs in the treatment of smear-positive TB patients [14]. On these grounds, application of the PCR assay only to smear-positive specimens would be reasonable. The present findings indicate that the +PCR smear-positive strategy is clearly cost-effective compared with the NOPCR strategy. Rapid differentiation between *M. tuberculosis* and nontuberculous mycobacteria by PCR results in infection control cost-savings by reducing inpatient care days and unnecessary isolations. Furthermore, needless contact tracing and patient distress are avoided, which were not measured in this study. However, as mentioned, application of the +PCR smear-positive strategy would require centralised specimen testing.

The absence of MDR cases in the model did not influence the cost-effectiveness evaluation because the PCR assay does not differentiate between drug-sensitive and MDR TB. Costs of treating MDR patients or suspects were thereby equal, regardless of the laboratory strategy chosen. Molecular rifampin resistance testing was not included in this model.

Costs included in the decision tree were those prevailing in Finnish healthcare. These and clinical practice patterns used in the model may vary between countries. The cost of the PCR kit may differ depending on the supplier, and the use of homemade kits and the sensitivity of the test applied is influenced by the extraction, amplification and final interpretation methods of the results used. Finally, a notable factor contributing interpretation of the results is the incidence of nontuberculous mycobacteria and its portion of the smear-positive patient population.

According to the present results, routine application of polymerase chain reaction testing to all specimens from suspected tuberculosis patients in a low-prevalence setting is not cost-saving. However, reduction of polymerase chain reaction assay expenses and more selective screening of the patient population would contribute to cost reductions compared with the no polymerase chain reaction strategy. If the polymerase chain reaction assay were applied only to smear-positive sputum specimens, the polymerase chain reaction smear-positive strategy would be the dominant strategy, that is, less costly and more effective in leading to correct treatment decisions and isolations. Polymerase

chain reaction testing would be particularly beneficial in populations with a high prevalence of nontuberculous mycobacteria.

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